ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Repatha 140 mg solution for injection in pre-filled syringe
Repatha 140 mg solution for injection in pre-filled pen
Repatha 420 mg solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Repatha 140 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 140 mg of evolocumab in 1 mL of solution.

Repatha 140 mg solution for injection in pre-filled pen

Each pre-filled pen contains 140 mg of evolocumab in 1 mL of solution.

Repatha 420 mg solution for injection in cartridge

Each cartridge contains 420 mg of evolocumab in 3.5 mL of solution (120 mg/mL).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Solution for injection (injection) in pre-filled pen (SureClick).
Solution for injection (injection) (automated mini-doser).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia and mixed dyslipidaemia

Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, and in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Established atherosclerotic cardiovascular disease

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.

4.2 Posology and method of administration

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

Posology

Primary hypercholesterolaemia and mixed dyslipidaemia (including heterozygous familial hypercholesterolaemia)

Adults and paediatric patients (aged 10 years and over)
The recommended dose of evolocumab is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Homozygous familial hypercholesterolaemia in adults and paediatric patients aged 10 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.

Established atherosclerotic cardiovascular disease in adults
The recommended dose of evolocumab is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Special populations

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

Patients with renal impairment
No dose adjustment is necessary in patients with renal impairment (see section 5.2).

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.

Paediatric population
The safety and effectiveness of Repatha have not been established in paediatric patients with heterozygous familial hypercholesterolaemia (HeFH) or homozygous familial hypercholesterolaemia (HoFH) who are younger than 10 years old or in paediatric patients with other types of hyperlipidaemia.

Method of administration

Subcutaneous use.

Evolocumab 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 must not be administered intravenously or intramuscularly.

Repatha 140 mg solution for injection in pre-filled syringe
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.

Repatha 140 mg solution for injection in pre-filled pen
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.

Repatha 420 mg solution for injection in cartridge
The 420 mg dose should be delivered using a single cartridge with the automated mini-doser.

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

For single use only.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 class C) have not been studied (see section 5.2). Evolocumab should be used with caution in patients with severe hepatic impairment.

Dry natural rubber

Repatha 140 mg solution for injection in pre-filled syringe
The needle cover of the glass pre-filled syringe 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 essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The pharmacokinetic interaction between statins and evolocumab was evaluated in the 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.

No studies on pharmacokinetic and pharmacodynamics interaction between evolocumab and lipid-lowering medicinal products 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 Repatha in pregnant women.

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

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 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

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions 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 hypercholesterolaemia population was consistent with that demonstrated in the primary hypercholesterolaemia and mixed dyslipidaemia 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[1]	Common
	Influenza-like illness	Uncommon

[1] See section Description of selected adverse reactions.

The safety profile was consistent between subjects with post-baseline LDL-C < 25 mg/dL (0.65 mmol/L) or < 40 mg/dL(1.03 mmol/L) compared to subjects with higher post-baseline LDL-C (≥ 40 mg/dL[1.03 mmol/L]), with median (Q1, Q3) Repatha exposure of 84.2 (78.1, 89.8) months in subjects who continued on Repatha and 59.8 (52.8, 60.3) months in subjects on placebo who switched to Repatha in an open-label extension study.

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

The safety and effectiveness of Repatha have been established in paediatric patients with heterozygous and homozygous familial hypercholesterolaemia. A clinical study to evaluate the effects of Repatha was conducted in 158 paediatric patients aged ≥ 10 to < 18 years old with heterozygous familial hypercholesterolaemia. No new safety concerns were identified and the safety data in this paediatric population was consistent with the known safety profile of the product in adults with heterozygous familial hypercholesterolaemia. Twenty-six paediatric patients with homozygous familial hypercholesterolaemia have been treated with Repatha in clinical studies conducted in patients aged ≥ 10 to < 18 years. No difference in safety was observed between paediatric and adult patients with homozygous familial hypercholesterolaemia.

Elderly population

Of the 18,546 patients treated with evolocumab 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 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.

The development of anti-evolocumab antibodies was not detected in clinical trials of paediatric patients treated with Repatha.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

There is no specific treatment for evolocumab 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: lipid modifying agents, 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 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 140 mg or 420 mg evolocumab 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. 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 resulted in a similar reduction of LDL-C when used alone or in combination with other lipid-lowering therapies.

Clinical efficacy in primary hypercholesterolaemia and mixed dyslipidaemia

LDL-C reduction of approximately 55% to 75% was achieved with evolocumab 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 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 demonstrated a $\geq$ 50% reduction in LDL-C at the mean of weeks 10 and 12. Up to 99% of patients treated with either dose of evolocumab 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 in combination with statins (rosuvastatin, simvastatin or atorvastatin). Evolocumab was compared to placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group.

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 ($p < 0.001$). 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. Repatha significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo ($p < 0.001$). 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 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)	-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 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. Repatha significantly reduced LDL-C compared with ezetimibe ($p < 0.001$). 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).

Treatment in the absence of a statin

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

Table 3. Treatment effects of evolocumab 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 (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 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. 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.

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 ($p < 0.001$) (see table 4).

Table 4. Treatment effects of evolocumab 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 were two randomised, controlled, open-label extension studies to assess the long-term safety and efficacy of Repatha in patients who completed treatment in a 'parent' study. In each extension study, patients were randomised 2:1 to receive either 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 entered the all Repatha period in which all patients received open-label Repatha for either another 4 years (OSLER) or 2 years (OSLER-2).

A total of 1,324 patients enrolled in OSLER. 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 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. Repatha 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. 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 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 Repatha at the beginning of OSLER or OSLER-2 without evidence of rebound.

TAUSSIG was a multicentre, open-label, 5-year extension study to assess the long-term safety and efficacy of Repatha, as an adjunct to other lipid-lowering therapies, in patients with severe familial hypercholesterolaemia (FH), including homozygous familial hypercholesterolaemia. A total of 194 severe familial hypercholesterolaemia (non-HoFH) patients and 106 homozygous familial hypercholesterolaemia patients enrolled in TAUSSIG. All patients in the study were initially treated with Repatha 420 mg once monthly, except for those receiving lipid apheresis at enrolment who began with 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 Repatha demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with severe familial hypercholesterolaemia (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 Repatha administration in patients with severe familial hypercholesterolaemia (non-HoFH).

Table 5. Effect of evolocumab on LDL-C in patients with severe familial hypercholesterolaemia (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 hypercholesterolaemia (non-HoFH) final analysis set.

Treatment of heterozygous familial hypercholesterolaemia in paediatric patients

HAUSER-RCT was a randomized, multicentre, placebo-controlled, double-blind, parallel-group, 24-week trial in 158 paediatric patients aged 10 to < 18 years with heterozygous familial hypercholesterolaemia. 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 up titration). Enrolled patients were randomized in a 2:1 ratio to receive 24 weeks of subcutaneous once monthly 420 mg Repatha or placebo.

The primary efficacy endpoint in this trial was percent change from baseline to week 24 in LDL-C. The difference between Repatha and placebo in mean percent change in LDL-C from baseline to week 24 was 38% (95% CI: 45%, 31%; $p < 0.0001$). The least squares mean Standard Error (SE) reduction ($p < 0.0001$) in LDL-C from baseline at week 24 was 44% (2%) in the Repatha group and

6% (3%) in the placebo group. Mean absolute LDL-C values at week 24 were 104 mg/dL in the Repatha group and 172 mg/dL in the placebo group. Reductions in LDL-C were observed by the first post-baseline assessment at the week 12 time point and were maintained throughout the trial.

The secondary endpoint of this trial was mean percent change from baseline to weeks 22 and 24 in LDL-C, where week 22 reflects the peak and week 24 the trough of the subcutaneous once monthly dosing interval, and provides information about the time-averaged effect of Repatha therapy over the entire dosing interval. The least squares mean treatment difference between Repatha and placebo in mean percent change in LDL-C from baseline to the mean of week 22 and week 24 was 42% (95% CI: 48%, 36%; p < 0.0001). For additional results, see table 6.

Table 6. Treatment effects of Repatha 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 Paediatric 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)

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.

HAUSER-OLE was an open-label, single-arm, multicentre, 80 week study of Repatha in 150 paediatric patients aged 10 to 17 years with HeFH that rolled-over from HAUSER-RCT and enrolled 13 *de novo* paediatric HoFH patients. Patients had to be on a low-fat diet and receiving background lipid-lowering therapy. All HeFH patients in this study received 420 mg Repatha subcutaneously once monthly (median exposure duration: 18.4 months). The mean (SE) percent changes in calculated LDL-C from baseline were: -44.4% (1.7%) at week 12, -41.0% (2.1%) at week 48, and -35.2% (2.5%) at week 80.
The mean (SE) percent change from baseline to week 80 in other lipid endpoints were: -32.1% (2.3%) non-HDL-C, -25.1% (2.3%) ApoB, -28.5% (2.0%) TC/HDL-C ratio, -30.3% (2.2%) ApoB/ApoA1 ratio, and -24.9% (1.9%) TC.

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. 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) (see table 7). Changes in other lipid parameters (TC, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a treatment effect of Repatha administration in patients with homozygous familial hypercholesterolaemia.

Table 7. Treatment effects of evolocumab 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 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 10% to 30% in patients with homozygous familial hypercholesterolaemia on apheresis (see table 8). Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of long-term Repatha administration in patients with homozygous familial hypercholesterolaemia. Reductions in LDL-C and changes in other lipid parameters in 14 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 8. Effect of evolocumab on LDL-C in patients with homozygous familial hypercholesterolaemia - 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 values at specific schedule visit (n) in the HoFH final analysis set.

HAUSER-OLE was an open-label, single-arm, multicentre, 80-week trial in 12 HofH subjects to evaluate the safety, tolerability and efficacy of Repatha for LDL-C reduction in paediatric patients from aged ≥ 10 to < 18 years of age with homozygous familial hypercholesterolaemia. Patients had to be on a low-fat diet and receiving background lipid-lowering therapy. All patients in the study received 420 mg Repatha subcutaneously once monthly. Median (Q1, Q3) LDL-C at baseline was 398 (343, 475) mg/dL. The median (Q1, Q3) percent change in LDL-C from baseline to week 80 was -14% (-41, 4). Reductions in LDL-C were observed by the first assessment at week 12 and was maintained throughout the trial, median (Q1, Q3) reductions ranging between 12% (-3, 32) and 15% (-4, 39). For additional results, please see table 9.

Table 9. Treatment effects of evolocumab compared with placebo in patients with homozygous familial hypercholesterolaemia – 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 Paediatric 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)

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.

Effect on atherosclerotic disease burden

The effects of 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. 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 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 Repatha or placebo respectively. The study did not investigate the correlation between atherosclerotic disease regression and cardiovascular events.

Effect on coronary atherosclerotic plaque morphology

The effects of Repatha 420 mg once monthly on coronary atherosclerotic plaques as assessed by optical coherence tomography (OCT), were evaluated in a 52-week double-blind, randomised, placebo controlled study including adult patients initiated within 7 days of a non-ST-segment elevation acute coronary syndrome (NSTEACS) on maximally tolerated statin therapy. For the primary endpoint of absolute change in minimum FCT (fibrous cap thickness) in a matched segment of artery from baseline, least squares (LS) mean (95% CI) increased from baseline by 42.7 μm (32.4, 53.1) in the Repatha group and 21.5 μm (10.9, 32.1) in the placebo group, an additional 21.2 μm (4.7, 37.7) compared to placebo ($p = 0.015$; 38% difference ($p = 0.041$)). The reported secondary findings show treatment differences including change in mean minimum FCT (increase 32.5 μm (12.7, 52.4); $p = 0.016$) and absolute change in maximum lipid arc (-26° (-49.6, -2.4); $p = 0.041$).

Cardiovascular risk reduction in adults with established atherosclerotic cardiovascular disease

The Repatha Outcomes Study (FOURIER) was a randomised, 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 randomised 1:1 to either Repatha (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 (see section 4.8); 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.

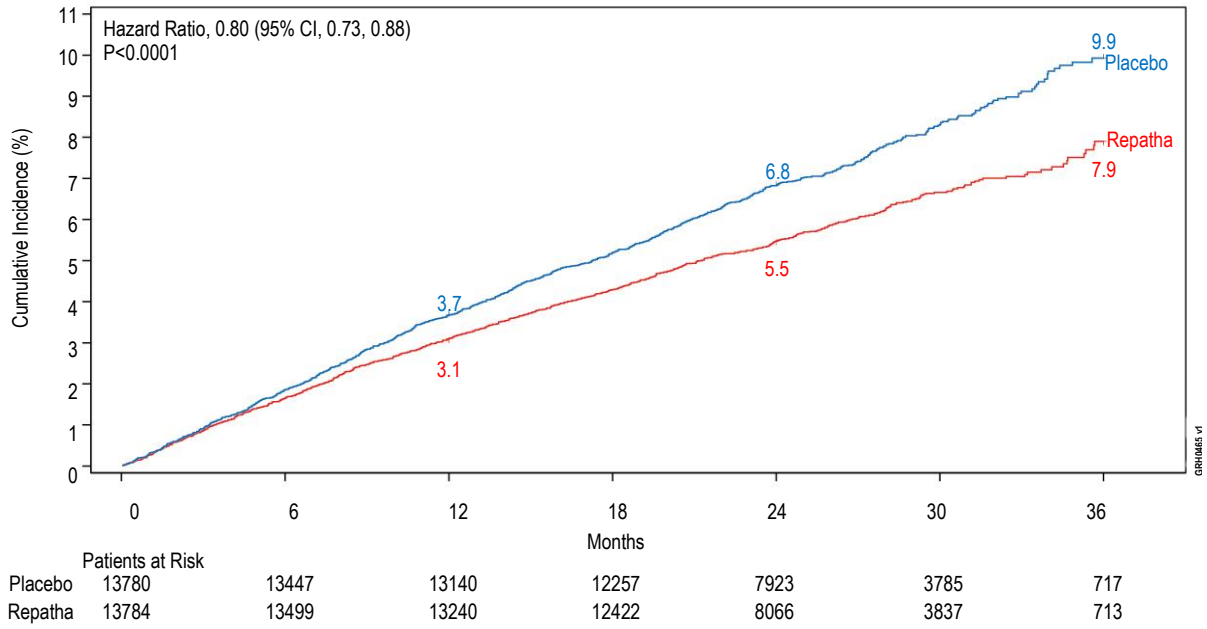
Repatha significantly reduced the risk of cardiovascular events defined as the composite of time to first CV death, MI, stroke, coronary revascularisation, or hospitalisation for unstable angina (see table 10); the Kaplan-Meier curves for the primary and key secondary composite endpoints separated at approximately 5 months (see figure 1 for the MACE three year Kaplan-Meier curve). The relative risk of the MACE composite (CV death, MI, or stroke) 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 revascularisation; 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 evolocumab on major cardiovascular events

	Placebo (N = 13,780) n (%)	**Evolocumab (N = 13,784) n (%)**	**Hazard ratio[a] (95% CI)**	**p value[b]**
MACE+ (composite of MACE, coronary revascularisation, or hospitalisation 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 revascularisation	965 (7.00)	759 (5.51)	0.78 (0.71, 0.86)	< 0.0001[c]
Hospitalisation 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 randomisation stratification factors collected via Interactive Voice Response System (IVRS).
[b] 2-sided log-rank test stratified by randomisation stratification factors collected via IVRS.
[c] Nominal significance.
[d] The treatment effect on stroke was driven by a reduction in risk of ischaemic stroke; there was no effect on haemorrhagic or undetermined stroke.
[e] Assessment of time to hospitalisation for unstable angina was *ad-hoc*.

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



FOURIER-OLE (study 1 and study 2) consisted of two open-label, single-arm, multicenter, extension studies to evaluate the long-term safety, tolerability, and efficacy of Repatha in patients with established cardiovascular disease who completed the FOURIER study. Enrolled patients received Repatha 140 mg every 2 weeks or 420 mg once monthly for approximately 5 years and continued moderate- (22.2%) or high-intensity (74.8%) background statin therapy. Of the 5 031 patients who received at least one dose of Repatha in study 1, 2 499 patients received Repatha and 2 532 patients received placebo in the FOURIER study. Of the 1 599 patients who received at least one dose of Repatha in study 2 854 patients received Repatha and 745 patients received placebo in the FOURIER study. Upon completion of study 1 and study 2, patients randomized to Repatha in the FOURIER study had up to 8.4 years (median 85.4 months) and 8.0 years of total Repatha exposure median 80.2 months) and patients randomized to placebo had up to 5.25 years (median 60.0 months) and 4.9 years of total Repatha exposure (median 55.1 months), respectively.

In study 1 and 2 combined, 72.4% (n = 4 802) of patients achieved a lowest post-baseline LDL-C < 25 mg/dL (0.65 mmol/L), 87.0% (n = 5 765) of patients achieved an LDL-C < 40 mg/dL (1.03 mmol/L), and 11.9% (n = 792) of patients had an all post-baseline LDL-C ≥ 40 mg/dL (1.03 mmol/L). Of the patients who achieved post-baseline low LDL-C (< 25 mg/dL or < 40 mg/dL), the overall subject incidences of treatment emergent adverse events were 80.0% patients who achieved LDL-C < 25 mg/dL and 82.7% in patients who achieved LDL-C < 40 mg/dL compared to 85.0% in patients with LDL-C ≥ 40 mg/dL. The overall subject incidences of serious treatment emergent adverse events were 37.7% in patients who achieved LDL-C < 25 mg/dL and 40.0% in patients who achieved LDL-C < 40 mg/dL compared to 41.5% in patients with LDL-C ≥ 40 mg/dL.

The mean percent reduction from baseline in LDL-C was stable during the OLE study period and ranged from 53.4% to 59.1% for study 1 and 62.5% to 67.2% for study 2, regardless of the patient's original randomised treatment group in the FOURIER study. This appears to translate into a numerically lower subject incidence rate of adjudicated exploratory CV endpoints of the composite of CV death, MI and stroke for patients who had received Repatha in both the FOURIER and FOURIER OLE studies compared with patients who had received placebo in the FOURIER study and Repatha in the FOURIER OLE studies.

Overall, no new safety findings were identified in these studies.

Effect on LDL-C during acute phase of Acute Coronary Syndromes (ACS)

EVOPACS was a single country, multicentre, double-blind, randomized, placebo-controlled, 8-week study on 308 ACS patients with evolocumab initiated in-hospital within 24 to 72 hours of presentation.

If patients were not on a statin or were on statin treatment other than atorvastatin 40 mg prior to screening, this was stopped and atorvastatin 40 mg once daily was initiated. Randomisation was stratified by study centre and presence of stable statin treatment within ≥ 4 weeks prior to enrolment. Most subjects (241 [78%]) were not on stable statin treatment for ≥ 4 weeks prior to screening and most (235 [76%]) were not taking a statin at baseline. By week 4, 281 (97%) subjects were receiving high-intensity statins. Evolocumab 420 mg once monthly significantly reduced LDL-C from baseline to week 8 compared with placebo ($p < 0.001$). The mean (SD) reduction in calculated LDL-C from baseline at week 8 was 77.1% (15.8%) in the evolocumab group and 35.4% (26.6%) in the placebo group with a least squares (LS) mean difference (95% CI) of 40.7% (36.2%, 45.2%). Baseline LDL-C values were 3.61 mmol/L (139.5 mg/dL) in the evolocumab group and 3.42 mmol/L (132.2 mg/dL) in the placebo group. LDL-C reductions in this study were consistent with previous studies where evolocumab was added to stable lipid-lowering therapy as demonstrated by on-treatment LDL-C levels at week 8 in this study (reflecting steady-state effect of high-intensity statin in both treatment arms) of 0.79 mmol/L (30.5 mg/dL) and 2.06 mmol/L (79.7 mg/dL) in the evolocumab plus atorvastatin and the placebo plus atorvastatin groups, respectively.

The effects of evolocumab in this patient population were consistent with those observed in previous studies in evolocumab clinical development program and no new safety concerns were noted.

5.2 Pharmacokinetic properties

Absorption and distribution

Following a single subcutaneous dose of 140 mg or 420 mg evolocumab 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 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 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 renal impairment. Data from the evolocumab 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.

In a clinical trial of 18 patients with either normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2, n = 6), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, n = 6), or end-stage renal disease (ESRD) receiving haemodialysis (n = 6), exposure to unbound evolocumab as assessed by C_{max} after a single 140 mg subcutaneous dose was decreased by 30% in patients with severe renal impairment and by 45% in patients with ESRD receiving haemodialysis. Exposure as assessed by AUC_{last} was decreased by approximately 24% in patients with severe renal impairment and by approximately 45% in patients with ESRD receiving haemodialysis. The exact mechanism of PK differences is unknown; however, differences in body weight could not explain these differences. Some factors including small sample size and large inter-subject variability should be considered when interpreting the results. The pharmacodynamics and safety of evolocumab in patients with severe renal impairment and ESRD were similar to patients with normal renal function, and there were no clinically meaningful differences in LDL-C lowering. Therefore, no dose adjustments are necessary in patients with severe renal impairment or ESRD receiving haemodialysis.

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). Single 140 mg subcutaneous doses of evolocumab 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 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.

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

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

Repatha 140 mg solution for injection in pre-filled syringe

3 years.

Repatha 140 mg solution for injection in pre-filled pen

3 years.

Repatha 420 mg solution for injection in cartridge

2 years.

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

6.4 Special precautions for storage

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

Repatha 140 mg solution for injection in pre-filled syringe

Store in the original carton in order to protect from light.

Repatha 140 mg solution for injection in pre-filled pen

Store in the original carton in order to protect from light.

Repatha 420 mg solution for injection in cartridge

Store in the original carton in order to protect from light and moisture.

6.5 Nature and contents of container

Repatha 140 mg solution for injection in pre-filled syringe

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.

Repatha 140 mg solution for injection in pre-filled pen

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

Pack sizes of one, two, three pre-filled pens or multipacks containing 6 (3 packs of 2) pre-filled pens.

Repatha 420 mg solution for injection in cartridge

A 3.5 mL solution in a single use cartridge made from cyclic olefin polymer with elastomer septum and piston as product-contact materials, and a resin cap. The pre-filled cartridge is assembled with a telescopic screw device component. The cartridge assembly is co-packed with an administration device. The fluid path within the administration device is made from stainless steel and non-DEHP polyvinyl chloride, with a stainless steel 29 gauge needle. The administration device contains silver oxide-zinc batteries and includes an adhesive patch made from polyester tape with an acrylate adhesive. The administration device is designed for use only with the provided 3.5 mL pre-filled cartridge assembly.

Pack sizes of one cartridge/automated mini-doser or multipack of three (3x1) cartridges/automated mini-dosers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Repatha 140 mg solution for injection in pre-filled syringe

EU/1/15/1016/001 - 1 pre-filled syringe

Repatha 140 mg solution for injection in pre-filled pen

EU/1/15/1016/002 - 1 pre-filled pen
EU/1/15/1016/003 - 2 pre-filled pens
EU/1/15/1016/004 - 3 pre-filled pens
EU/1/15/1016/005 - 6 (3x2) pre-filled pens (multipack)

Repatha 420 mg solution for injection in cartridge

EU/1/15/1016/006 - 1 cartridge with co-packed automated mini-doser
EU/1/15/1016/007 - 3 (3x1) cartridges with co-packed automated mini-dosers (multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2015
Date of latest renewal: 14 April 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Amgen Manufacturing Limited LLC
Road 31 km 24.6
Juncos
Puerto Rico, 00777
United States

Immunex Rhode Island Corporation
40 Technology Way
West Greenwich
Rhode Island, 02817
United States

Name and address of the manufacturers responsible for batch release

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Repatha 140 mg solution for injection in pre-filled syringe
evolocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 140 mg of evolocumab in 1 mL of solution.

3. LIST OF EXCIPIENTS

Proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 pre-filled syringe.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains latex, read the package leaflet before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1016/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Repatha 140 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Repatha 140 mg solution for injection
evolocumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Repatha 140 mg injection
evolocumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Repatha 140 mg solution for injection in pre-filled pen
evolocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 140 mg of evolocumab in 1 mL of solution.

3. LIST OF EXCIPIENTS

Proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 SureClick pre-filled pen.
2 SureClick pre-filled pens.
3 SureClick pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1016/002
EU/1/15/1016/003
EU/1/15/1016/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Repatha 140 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Repatha 140 mg solution for injection in pre-filled pen
evolocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 140 mg of evolocumab in 1 mL of solution.

3. LIST OF EXCIPIENTS

Proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
Multipack: 6 (3 packs of 2) SureClick pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1016/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Repatha 140 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Repatha 140 mg solution for injection in pre-filled pen
evolocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 140 mg of evolocumab in 1 mL of solution.

3. LIST OF EXCIPIENTS

Proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
2 SureClick pre-filled pens. Component of a multi-pack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1016/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Repatha 140 mg pen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Repatha 140 mg injection
evolocumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON AUTOMATED MINI-DOSER

1. NAME OF THE MEDICINAL PRODUCT

Repatha 420 mg solution for injection in cartridge
evolocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each cartridge contains 420 mg of evolocumab in 3.5 mL of solution (120 mg/mL).

3. LIST OF EXCIPIENTS

Proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 cartridge and automated mini-doser.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1016/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Repatha 420 mg cartridge

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Repatha 420 mg solution for injection in cartridge
evolocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each cartridge contains 420 mg of evolocumab in 3.5 mL of solution (120 mg/mL).

3. LIST OF EXCIPIENTS

Proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
Multipack: 3 (3 packs of 1) cartridges and automated mini-dosers.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1016/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Repatha 420 mg cartridge

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Repatha 420 mg solution for injection in cartridge
evolocumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each cartridge contains 420 mg of evolocumab in 3.5 mL of solution (120 mg/mL).

3. LIST OF EXCIPIENTS

Proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 cartridge and automated mini-doser. Component of a multi-pack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1016/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Repatha 420 mg cartridge

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Repatha 420 mg injection
evolocumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Repatha 140 mg solution for injection in pre-filled syringe
evolocumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- The warnings and instructions in this document are intended for the person taking the medicine. If you are a parent or carer responsible for giving the medicine to someone else, such as a child, you will need to apply the information accordingly

What is in this leaflet

1. What Repatha is and what it is used for

What Repatha is and how it works

Repatha is a medicine that lowers levels of 'bad' cholesterol, a type of fat, in the blood.

Repatha contains the active substance evolocumab, a monoclonal antibody (a type of specialised protein designed to attach to a target substance in the body). Evolocumab is designed to attach to a substance called PCSK9 that affects the liver's ability to take in cholesterol. By attaching to, and mopping up PCSK9, the medicine increases the amount of cholesterol entering the liver and so lowers the level of cholesterol in the blood.

What Repatha is used for

Repatha is used in addition to your cholesterol lowering diet if you are:
- an adult with a high cholesterol level in your blood (primary hypercholesterolaemia [heterozygous familial and non-familial] or mixed dyslipidaemia). It is given:
  - together with a statin or other cholesterol lowering medication, if the maximum dose of a statin does not lower levels of cholesterol sufficiently.
  - alone or together with other cholesterol lowering medications when statins do not work well or cannot be used.
- a child aged 10 years and older with a high cholesterol level in your blood because of a condition that runs in your family (heterozygous familial hypercholesterolaemia or HeFH). It is given alone or together with other cholesterol lowering treatments

- an adult or a child aged 10 years and older with a high cholesterol level in your blood because of a condition that runs in your family (homozygous familial hypercholesterolaemia or HoFH). It is given together with other cholesterol lowering treatments
- an adult with a high cholesterol level in your blood and established atherosclerotic cardiovascular disease (a history of heart attack, stroke or blood vessel problems). It is given:
  - together with a statin or other cholesterol lowering medication, if the maximum dose of a statin does not lower levels of cholesterol sufficiently.
  - alone or together with other cholesterol lowering medications when statins do not work well or cannot be used.

Repatha is used in patients who cannot control their cholesterol levels with a cholesterol lowering diet alone. You should stay on your cholesterol lowering diet while taking this medicine. Repatha can help prevent heart attack, stroke, and certain heart procedures to restore blood flow to the heart due to a build-up of fatty deposits in your arteries (also known as atherosclerotic cardiovascular disease).

2. What you need to know before you use Repatha

Do not use Repatha if you are allergic to evolocumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Repatha if you have liver disease.

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

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

Children and adolescents

The use of Repatha has been studied in children 10 years of age and older being treated for heterozygous or homozygous familial hypercholesterolaemia.

The use of Repatha has not been studied in children under 10 years of age.

Other medicines and Repatha

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Repatha has not been tested in pregnant women. It is not known if Repatha will harm your unborn baby.

It is not known whether Repatha is found in breast milk.

It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Repatha, considering the benefit of breast-feeding to the baby and the benefit of Repatha to the mother.

Driving and using machines

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

Repatha contains sodium

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

3. How to use Repatha

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose depends on the underlying condition:

- for adults with primary hypercholesterolaemia and mixed dyslipidaemia the dose is either 140 mg every two weeks or 420 mg once monthly.
- for children aged 10 years or older with heterozygous familial hypercholesterolaemia the dose is either 140 mg every two weeks or 420 mg once monthly.
- for adults or children aged 10 years or older with homozygous familial hypercholesterolaemia the recommended starting dose is 420 mg once monthly. After 12 weeks your doctor may decide to increase the dose to 420 mg every two weeks. If you also receive apheresis, a procedure similar to dialysis where cholesterol and other fats are removed from the blood, your doctor may decide to start you on a dose of 420 mg every two weeks to coincide with your apheresis treatment.
- for adults with established atherosclerotic cardiovascular disease (a history of heart attack, stroke or blood vessel problems) the dose is either 140 mg every two weeks or 420 mg once monthly.

Repatha is given as an injection under the skin (subcutaneous).

If your doctor prescribes a dose of 420 mg you must use three pre-filled syringes because each pre-filled syringe only contains 140 mg of medicine. After reaching room temperature, all injections should be given within a 30 minute period.

If your doctor decides that you or a caregiver can give the injections of Repatha, you or your caregiver should receive training on how to prepare and inject Repatha correctly. Do not try to inject Repatha until you have been shown how to do it by your doctor or nurse.

See the detailed "Instructions for Use" at the end of this leaflet for instructions about how to store, prepare, and give your Repatha injections at home.

Before starting Repatha, you should be on a diet to lower your cholesterol. You should keep on this cholesterol lowering diet while taking Repatha.

If your doctor has prescribed Repatha along with another cholesterol lowering medicine, follow your doctor's instructions on how to take these medicines together. In this case, please read the dosage instructions in the package leaflet of that particular medicine as well.

If you use more Repatha than you should

Contact your doctor or pharmacist immediately.

If you forget to take Repatha

Take Repatha as soon as you can after the missed dose. Then, contact your doctor who will tell you when you should schedule your next dose, and follow the new schedule exactly as your doctor has told you.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common (may affect up to 1 in 10 people)
- Flu (high temperature, sore throat, runny nose, cough and chills)
- Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections)
- Feeling sick (nausea)
- Back pain
- Joint pain (arthralgia)
- Muscle pain
- Injection site reactions, such as bruising, redness, bleeding, pain or swelling
- Allergic reactions including rash
- Headache

Uncommon (may affect up to 1 in 100 people)
- Hives, red itchy bumps on your skin (urticaria)
- Flu-like symptoms

Rare (may affect up to 1 in 1,000 people)
- Swelling of the face, mouth, tongue, or throat (angioedema)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Repatha

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original carton in order to protect from light.

Your pre-filled syringe may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. After removal from the refrigerator, Repatha may be stored at room temperature (up to 25°C) in the original carton and must be used within 1 month.

Do not use this medicine if you notice it is discoloured or contains large lumps, flakes or coloured particles.

Do not throw away any medicines via wastewater or household waste.

Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Repatha contains
- The active substance is evolocumab. Each pre-filled syringe contains 140 mg of evolocumab in 1 mL of solution.
- The other ingredients are proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

What Repatha looks like and contents of the pack

Repatha is a solution which is clear to opalescent, colourless to yellowish, and practically free from particles.

Each pack contains one single use pre-filled syringe.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Manufacturer
Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Manufacturer
Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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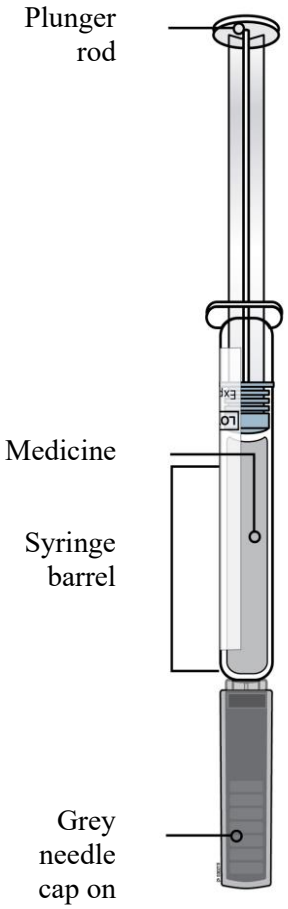
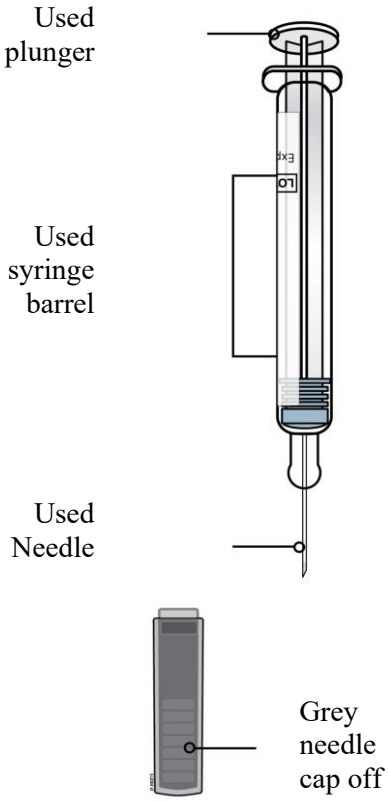
This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions for use: Repatha single use pre-filled syringe

Guide to parts	
Before use	After use
	
	Needle is inside.

Important

Before you use a single use Repatha pre-filled syringe, read this important information:

- **Do not** freeze or use the Repatha pre-filled syringe if it has been frozen.
- **Do not** use the Repatha pre-filled syringe if the packaging is open or damaged.
- **Do not** use the Repatha pre-filled syringe if it has been dropped onto a hard surface. Part of the syringe may be broken even if you cannot see the break. Use a new Repatha pre-filled syringe.
- **Do not** remove the grey needle cap from the Repatha pre-filled syringe until you are ready to inject.

Step 1: Prepare	
A	**Remove the Repatha pre-filled syringe carton from the refrigerator and wait 30 minutes.**
Wait at least 30 minutes for the pre-filled syringe in the carton to naturally reach room temperature before injecting. Check that the name Repatha appears on the carton label. • **Do not** try to warm the Repatha pre-filled syringe by using a heat source such as hot water or microwave.	
• **Do not** leave the Repatha pre-filled syringe exposed to direct sunlight.	
• **Do not** shake the Repatha pre-filled syringe.	

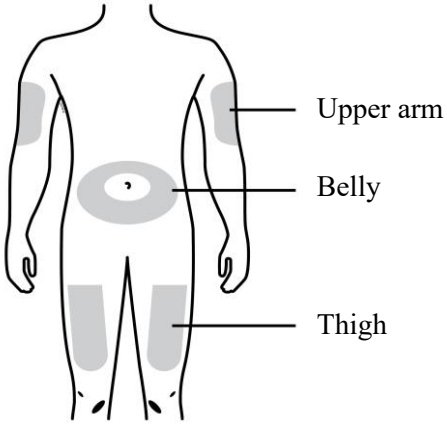
B	**Gather all materials needed for your injection.**

Wash your hands thoroughly with soap and water.

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

- One Repatha pre-filled syringe in its tray.
- Alcohol wipes.
- Cotton ball or gauze pad.
- Plaster.
- Sharps disposal container.
- **Do not** use if expiry date on the Repatha pre-filled syringe carton has passed.

C	**Choose your injection site.**

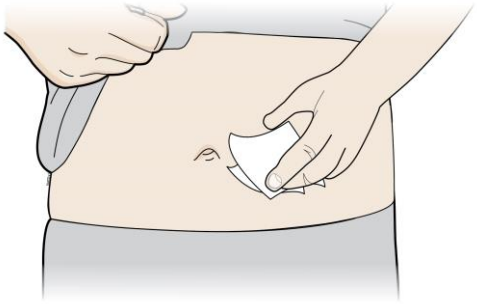


You can use:

- Thigh.
- Belly, except for the 2 inches (5 centimetres) around the belly button.
- Outer area of upper arm (only if someone else is giving you the injections).
- **Do not** choose an area where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

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.

D	**Clean your injection site.**



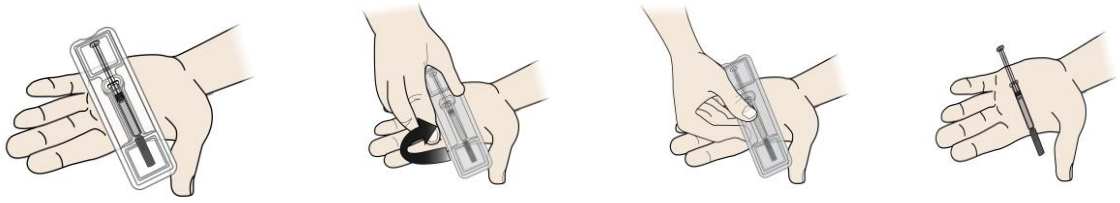
Clean your injection site with an alcohol wipe. Let your skin dry before injecting.

- **Do not** touch this area of skin again before injecting.

E	**Remove the pre-filled syringe from the tray.**

Turn tray over

Gently Press



To remove:

- Peel the paper off of the tray.
- Place the tray on your hand.
- Turn the tray over and gently press the middle of the tray's back to release the syringe into your palm.
- If the pre-filled syringe does not release from the tray, gently press on the back of tray.
- **Do not** pick up or pull the pre-filled syringe by the plunger rod or grey needle cap. This could damage the syringe.
- **Do not** remove the grey needle cap from the pre-filled syringe until you are ready to inject.

Always hold the pre-filled syringe by the syringe barrel.

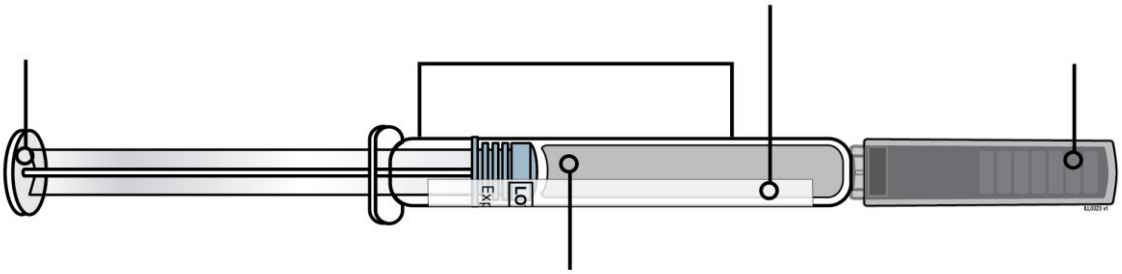
F	**Inspect medicine and syringe.**

Plunger rod

Syringe barrel

Syringe label with expiration date

Grey needle cap on

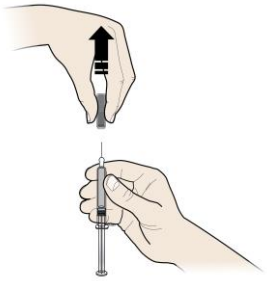


Medicine

Always hold the pre-filled syringe by the syringe barrel.
Check that:

- The name Repatha appears on the pre-filled syringe label.
- The medicine in the pre-filled syringe is clear and colourless to slightly yellow.
- **Do not** use the pre-filled syringe if any part of the pre-filled syringe appears cracked or broken.
- **Do not** use the pre-filled syringe if the grey needle cap is missing or not securely attached.
- **Do not** use the pre-filled syringe if the medicine is discoloured or contains large lumps, flakes or coloured particles.
- **Do not** use the pre-filled syringe if the expiration date on the pre-filled syringe has passed.

Step 2: Get ready	
A	**Carefully pull the grey needle cap straight out and away from your body. Do not** leave the grey needle cap off for more than 5 minutes. This can dry out the medicine.

1.	2.
	
It is normal to see a drop of medicine at the end of the needle.	Immediately place the cap in the sharps disposal container.

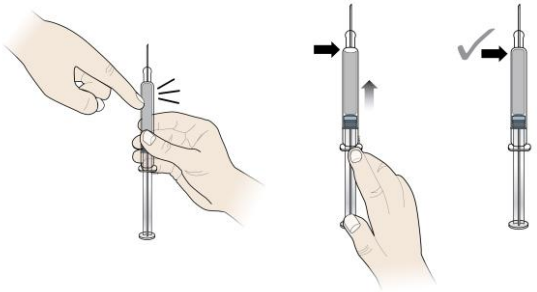
- **Do not** twist or bend the grey needle cap. This can damage the needle.
- **Do not** put the grey needle cap back onto the pre-filled syringe.

B	**Remove the air bubble / gap.**

You may notice an air bubble/gap in the Repatha pre-filled syringe.

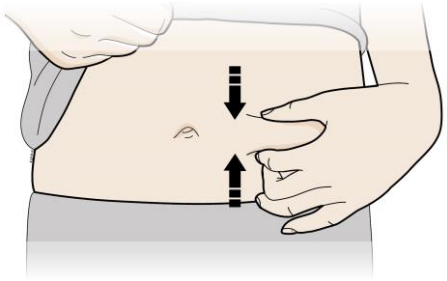
If you notice an air bubble/gap:

- Hold the pre-filled syringe with the needle facing up.
- Gently tap the syringe barrel with your fingers until the air bubble/gap rises to the top of the syringe.
- Slowly and gently push the plunger rod up to get the air out of the pre-filled syringe. Be very careful not to push out any medicine.



- **Do not** tap the syringe needle.

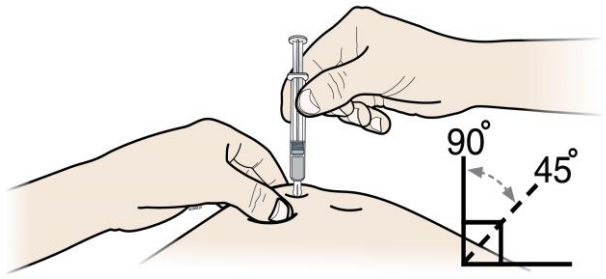
C	**PINCH your injection site to create a firm surface.**



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

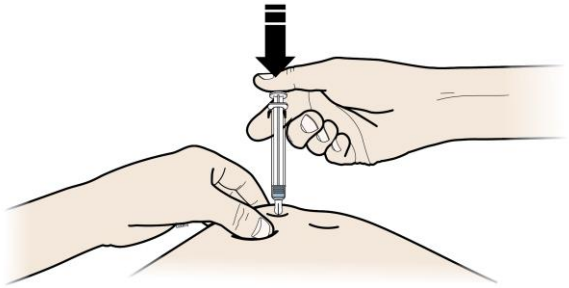
It is important to keep the skin pinched while injecting.

Step 3: Inject	
A	**Hold the PINCH. Insert the needle into the skin using a 45 to 90 degree angle.**

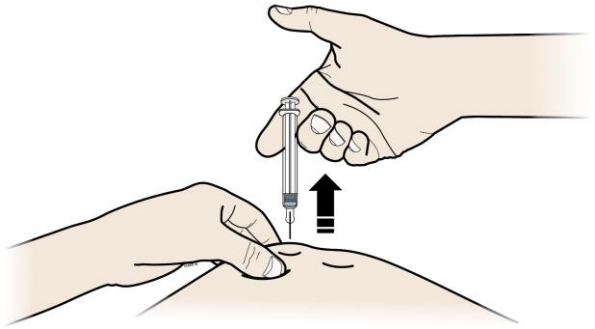


- **Do not** place your finger on the plunger rod while inserting the needle.

B	**Using slow and constant pressure, PUSH the plunger rod all the way down until the syringe is empty.**



C	**When done, RELEASE your thumb, and gently lift the syringe off skin.**



- **Do not** put the grey needle cap back onto the used syringe.

Step 4: Finish	
A	**Immediately place the used syringe in a sharps disposal container.**

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

- **Do not** reuse the used syringe.
- **Do not** use any medicine that is left in the used syringe.
- **Do not** recycle the syringe or the sharps disposal container or throw it into household rubbish.

Keep the used syringe and sharps container out of the sight and reach of children.

B	**Examine the injection site.**

If there is blood, press a cotton ball or gauze pad on your injection site. Apply a plaster if needed.

- **Do not** rub the injection site.

Package leaflet: Information for the user

Repatha 140 mg solution for injection in pre-filled pen
evolocumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- The warnings and instructions in this document are intended for the person taking the medicine. If you are a parent or carer responsible for giving the medicine to someone else, such as a child, you will need to apply the information accordingly.

What is in this leaflet

1. What Repatha is and what it is used for

What Repatha is and how it works

Repatha is a medicine that lowers levels of 'bad' cholesterol, a type of fat, in the blood.

Repatha contains the active substance evolocumab, a monoclonal antibody (a type of specialised protein designed to attach to a target substance in the body). Evolocumab is designed to attach to a substance called PCSK9 that affects the liver's ability to take in cholesterol. By attaching to, and mopping up PCSK9, the medicine increases the amount of cholesterol entering the liver and so lowers the level of cholesterol in the blood.

What Repatha is used for

Repatha is used in addition to your cholesterol lowering diet if you are:
- an adult with a high cholesterol level in your blood (primary hypercholesterolaemia [heterozygous familial and non-familial] or mixed dyslipidaemia). It is given:
  - together with a statin or other cholesterol lowering medication, if the maximum dose of a statin does not lower levels of cholesterol sufficiently.
  - alone or together with other cholesterol lowering medications when statins do not work well or cannot be used.
- a child aged 10 years and older with a high cholesterol level in your blood because of a condition that runs in your family (heterozygous familial hypercholesterolaemia or HeFH). It is given alone or together with other cholesterol lowering treatments.

- an adult or a child aged 10 years and older with a high cholesterol level in your blood because of a condition that runs in your family (homozygous familial hypercholesterolaemia or HoFH). It is given together with other cholesterol lowering treatments.
- an adult with a high cholesterol level in your blood and established atherosclerotic cardiovascular disease (a history of heart attack, stroke or blood vessel problems). It is given:
  - together with a statin or other cholesterol lowering medication, if the maximum dose of a statin does not lower levels of cholesterol sufficiently.
  - alone or together with other cholesterol lowering medications when statins do not work well or cannot be used.

Repatha is used in patients who cannot control their cholesterol levels with a cholesterol lowering diet alone. You should stay on your cholesterol lowering diet while taking this medicine. Repatha can help prevent heart attack, stroke, and certain heart procedures to restore blood flow to the heart due to a build-up of fatty deposits in your arteries (also known as atherosclerotic cardiovascular disease).

2. What you need to know before you use Repatha

Do not use Repatha if you are allergic to evolocumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Repatha if you have liver disease.

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

Children and adolescents

The use of Repatha has been studied in children 10 years of age and older being treated for heterozygous or homozygous familial hypercholesterolaemia.

The use of Repatha has not been studied in children under 10 years of age.

Other medicines and Repatha

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Repatha has not been tested in pregnant women. It is not known if Repatha will harm your unborn baby.

It is not known whether Repatha is found in breast milk.

It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Repatha, considering the benefit of breast-feeding to the baby and the benefit of Repatha to the mother.

Driving and using machines

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

Repatha contains sodium

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

3. How to use Repatha

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose depends on the underlying condition:

- for adults with primary hypercholesterolaemia and mixed dyslipidaemia the dose is either 140 mg every two weeks or 420 mg once monthly.
- for children aged 10 years or older with heterozygous familial hypercholesterolaemia the dose is either 140 mg every two weeks or 420 mg once monthly.
- for adults or children aged 10 years or older with homozygous familial hypercholesterolaemia the recommended starting dose is 420 mg once monthly. After 12 weeks your doctor may decide to increase the dose to 420 mg every two weeks. If you also receive apheresis, a procedure similar to dialysis where cholesterol and other fats are removed from the blood, your doctor may decide to start you on a dose of 420 mg every two weeks to coincide with your apheresis treatment.
- for adults with established atherosclerotic cardiovascular disease (a history of heart attack, stroke or blood vessel problems) the dose is either 140 mg every two weeks or 420 mg once monthly.

Repatha is given as an injection under the skin (subcutaneous).

If your doctor prescribes a dose of 420 mg you must use three pre-filled pens because each pre-filled pen only contains 140 mg of medicine. After reaching room temperature, all injections should be given within a 30 minute period.

If your doctor decides that you or a caregiver can give the injections of Repatha, you or your caregiver should receive training on how to prepare and inject Repatha correctly. Do not try to inject Repatha until you have been shown how to do it by your doctor or nurse.

See the detailed "Instructions for Use" at the end of this leaflet for instructions about how to store, prepare, and give your Repatha injections at home. If using the pre-filled pen, **place the correct (yellow) end of the pen on the skin before injecting.**

Before starting Repatha, you should be on a diet to lower your cholesterol. You should keep on this cholesterol lowering diet while taking Repatha.

If your doctor has prescribed Repatha along with another cholesterol lowering medicine, follow your doctor's instructions on how to take these medicines together. In this case, please read the dosage instructions in the package leaflet of that particular medicine as well.

If you use more Repatha than you should

Contact your doctor or pharmacist immediately.

If you forget to take Repatha

Take Repatha as soon as you can after the missed dose. Then, contact your doctor who will tell you when you should schedule your next dose, and follow the new schedule exactly as your doctor has told you.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common (may affect up to 1 in 10 people)
- Flu (high temperature, sore throat, runny nose, cough and chills)
- Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections)
- Feeling sick (nausea)
- Back pain
- Joint pain (arthralgia)
- Muscle pain
- Injection site reactions, such as bruising, redness, bleeding, pain or swelling
- Allergic reactions including rash
- Headache

Uncommon (may affect up to 1 in 100 people)
- Hives, red itchy bumps on your skin (urticaria)
- Flu-like symptoms

Rare (may affect up to 1 in 1,000 people)
- Swelling of the face, mouth, tongue, or throat (angioedema)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Repatha

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original carton in order to protect from light.

Your pre-filled pen may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. After removal from the refrigerator, Repatha may be stored at room temperature (up to 25°C) in the original carton and must be used within 1 month.

Do not use this medicine if you notice it is discoloured or contains large lumps, flakes or coloured particles.

Do not throw away any medicines via wastewater or household waste.

Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Repatha contains
- The active substance is evolocumab. Each SureClick pre-filled pen contains 140 mg of evolocumab in 1 mL of solution.
- The other ingredients are proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

What Repatha looks like and contents of the pack

Repatha is a solution which is clear to opalescent, colourless to yellowish, and practically free from particles.

Each pack contains one, two, three or six single use SureClick pre-filled pens.

Marketing Authorisation Holder and Manufacturer
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Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder
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Manufacturer
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

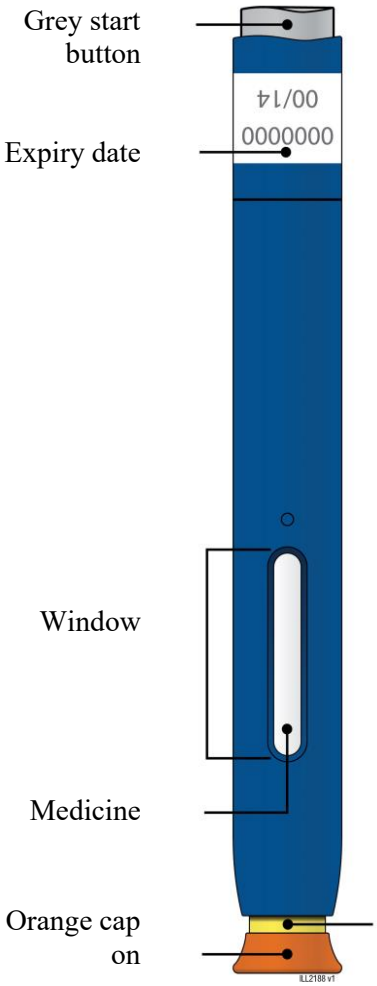
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

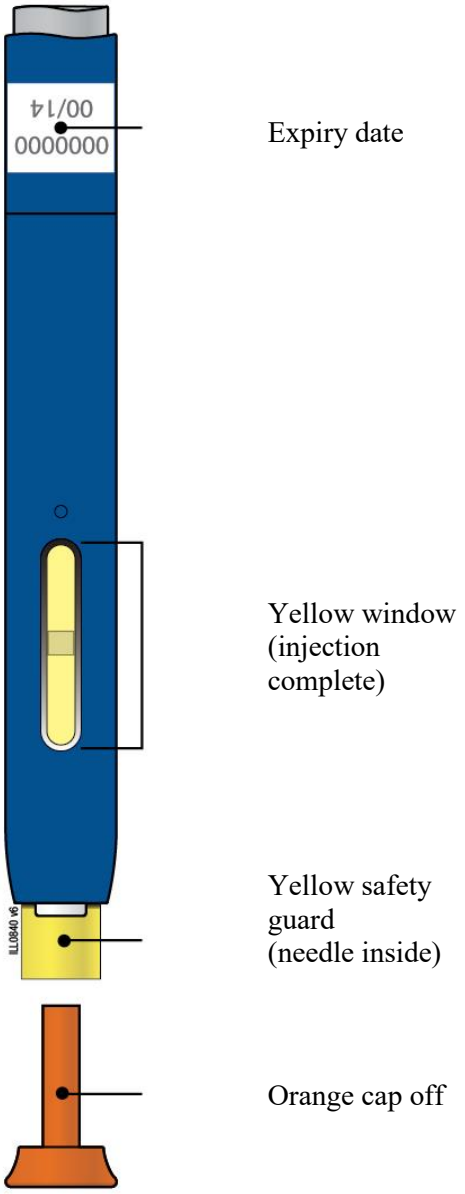
Instructions for use: Repatha single use SureClick pre-filled pen

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.

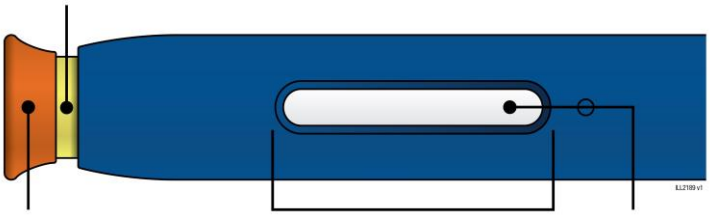
Step 1: Prepare	
A	**Remove one Repatha pre-filled pen from the package.**

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 pen 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.**

Yellow safety guard
(needle inside)



Orange cap on Window Medicine

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

Check the expiration date.

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

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

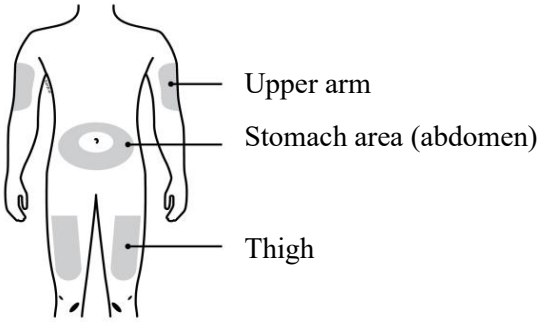
C	**Gather all materials needed for your injection.**

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.**



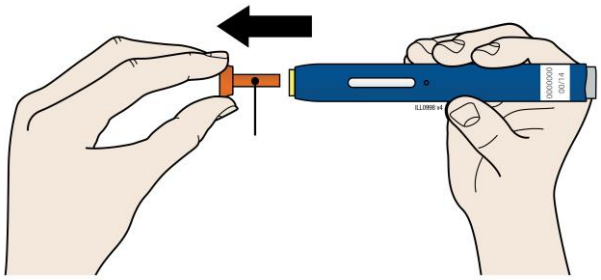
Only use these injection sites:

- 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

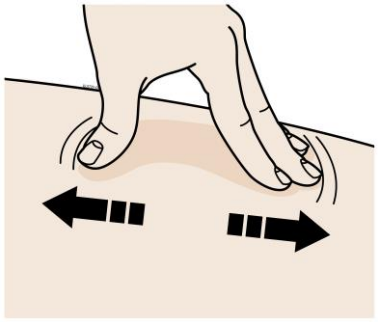
It is normal to see a drop of liquid at the end of the needle or yellow safety guard.

- **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.

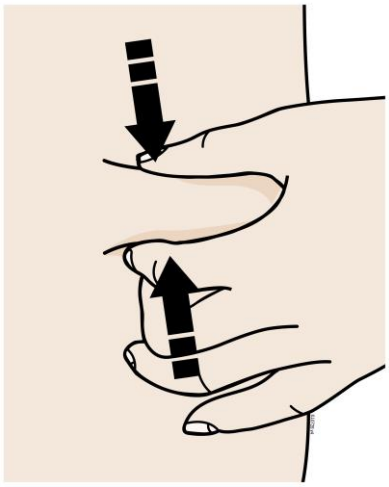
Stretch method



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

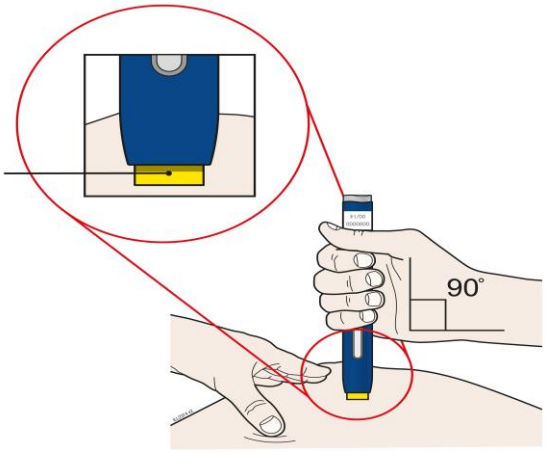


Pinch the skin firmly between your thumb and fingers, creating an area about 2 inches (5 centimetres) wide.

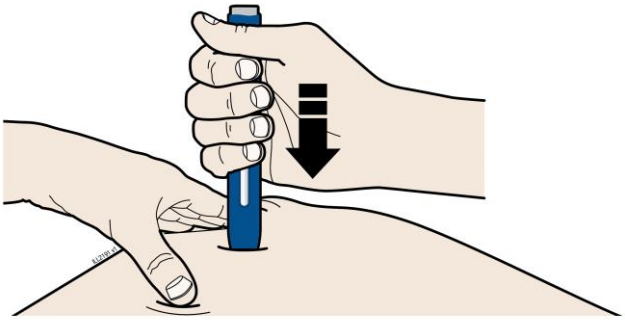
Important: It is important to keep skin stretched or pinched while injecting.

Step 3: Inject	
A	Keep holding the stretched or pinched skin. With the orange cap off, **put** the yellow safety guard on your 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)



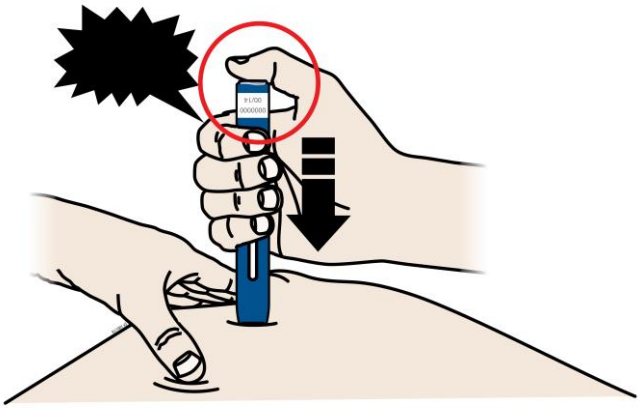
B	Firmly **push** down the pre-filled pen onto the skin until it stops moving.



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

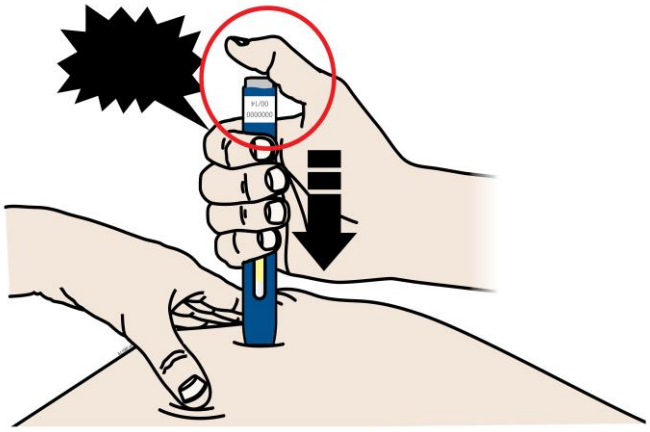
C	When you are ready to inject, **press** the grey start button. You will hear a **click**.

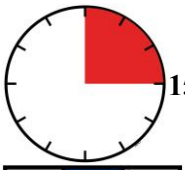
“click”



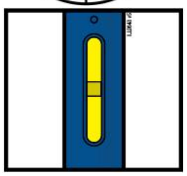
D	Keep **pushing** down on the skin. Then **lift** your thumb while still holding the pre-filled pen on your skin. Your injection could take about 15 seconds.

“click”

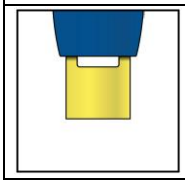




15 seconds



Window turns from clear to yellow when the injection is done. You may hear a second click.



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.

Package leaflet: Information for the user

Repatha 420 mg solution for injection in cartridge
evolocumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- The warnings and instructions in this document are intended for the person taking the medicine. If you are a parent or carer responsible for giving the medicine to someone else, such as a child, you will need to apply the information accordingly.

What is in this leaflet

1. What Repatha is and what it is used for

What Repatha is and how it works

Repatha is a medicine that lowers levels of 'bad' cholesterol, a type of fat, in the blood.

Repatha contains the active substance evolocumab, a monoclonal antibody (a type of specialised protein designed to attach to a target substance in the body). Evolocumab is designed to attach to a substance called PCSK9 that affects the liver's ability to take in cholesterol. By attaching to, and mopping up PCSK9, the medicine increases the amount of cholesterol entering the liver and so lowers the level of cholesterol in the blood.

What Repatha is used for

Repatha is used in addition to your cholesterol lowering diet if you are:
- an adult with a high cholesterol level in your blood (primary hypercholesterolaemia [heterozygous familial and non-familial] or mixed dyslipidaemia). It is given:
  - together with a statin or other cholesterol lowering medication, if the maximum dose of a statin does not lower levels of cholesterol sufficiently.
  - alone or together with other cholesterol lowering medications when statins do not work well or cannot be used.
- a child aged 10 years and older with a high cholesterol level in your blood because of a condition that runs in your family (heterozygous familial hypercholesterolaemia or HeFH). It is given alone or together with other cholesterol lowering treatments

- an adult or a child aged 10 years and older with a high cholesterol level in your blood because of a condition that runs in your family (homozygous familial hypercholesterolaemia or HoFH). It is given together with the other cholesterol lowering treatments.
- an adult with a high cholesterol level in your blood and established atherosclerotic cardiovascular disease (a history of heart attack, stroke or blood vessel problems). It is given:
  - together with a statin or other cholesterol lowering medication, if the maximum dose of a statin does not lower levels of cholesterol sufficiently.
  - alone or together with other cholesterol lowering medications when statins do not work well or cannot be used.

Repatha is used in patients who cannot control their cholesterol levels with a cholesterol lowering diet alone. You should stay on your cholesterol lowering diet while taking this medicine. Repatha can help prevent heart attack, stroke, and certain heart procedures to restore blood flow to the heart due to a build-up of fatty deposits in your arteries (also known as atherosclerotic cardiovascular disease).

2. What you need to know before you use Repatha

Do not use Repatha if you are allergic to evolocumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Repatha if you have liver disease.

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

Children and adolescents

The use of Repatha has been studied in children 10 years of age and older being treated for heterozygous or homozygous familial hypercholesterolaemia.

The use of Repatha has not been studied in children under 10 years of age.

Other medicines and Repatha

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Repatha has not been tested in pregnant women. It is not known if Repatha will harm your unborn baby.

It is not known whether Repatha is found in breast milk.

It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Repatha, considering the benefit of breast-feeding to the baby and the benefit of Repatha to the mother.

Driving and using machines

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

Repatha contains sodium

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

3. How to use Repatha

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose depends on the underlying condition:

- for adults with primary hypercholesterolaemia and mixed dyslipidaemia the dose is either 140 mg every two weeks or 420 mg once monthly.
- for children aged 10 years or older with heterozygous familial hypercholesterolaemia the dose is either 140 mg every two weeks or 420 mg once monthly.
- for adults or children aged 10 years or older with homozygous familial hypercholesterolaemia the recommended starting dose is 420 mg once monthly. After 12 weeks your doctor may decide to increase the dose to 420 mg every two weeks. If you also receive apheresis, a procedure similar to dialysis where cholesterol and other fats are removed from the blood, your doctor may decide to start you on a dose of 420 mg every two weeks to coincide with your apheresis treatment.
- for adults with established atherosclerotic cardiovascular disease (a history of heart attack, stroke or blood vessel problems) the dose is either 140 mg every two weeks or 420 mg once monthly.

Repatha is given as an injection under the skin (subcutaneous).

If your doctor decides that you or a caregiver can give the injections of Repatha using the automated mini-doser, you or your caregiver should receive training on how to prepare and inject Repatha correctly. Do not try to use the automated mini-doser until you have been shown how to do it by your doctor or nurse. It is recommended that 10 to 13 years olds are supervised by an adult when they are using the automated mini-doser.

See the detailed "Instructions for Use" at the end of this leaflet for instructions about how to store, prepare, and use your Repatha automated mini-doser at home.

Before starting Repatha, you should be on a diet to lower your cholesterol. You should keep on this cholesterol lowering diet while taking Repatha.

If your doctor has prescribed Repatha along with another cholesterol lowering medicine, follow your doctor's instructions on how to take these medicines together. In this case, please read the dosage instructions in the package leaflet of that particular medicine as well.

If you use more Repatha than you should

Contact your doctor or pharmacist immediately.

If you forget to take Repatha

Take Repatha as soon as you can after the missed dose. Then, contact your doctor who will tell you when you should schedule your next dose, and follow the new schedule exactly as your doctor has told you.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common (may affect up to 1 in 10 people)
- Flu (high temperature, sore throat, runny nose, cough and chills)
- Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections)
- Feeling sick (nausea)
- Back pain
- Joint pain (arthralgia)
- Muscle pain
- Injection site reactions, such as bruising, redness, bleeding, pain or swelling
- Allergic reactions including rash
- Headache

Uncommon (may affect up to 1 in 100 people)
- Hives, red itchy bumps on your skin (urticaria)
- Flu-like symptoms

Rare (may affect up to 1 in 1,000 people)
- Swelling of the face, mouth, tongue, or throat (angioedema)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Repatha

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original carton in order to protect from light and moisture.

Your medicine (cartridge and automated mini-doser) may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. After removal from the refrigerator, Repatha may be stored at room temperature (up to 25°C) in the original carton and must be used within 1 month.

Do not use this medicine if you notice it is discoloured or contains large lumps, flakes or coloured particles.

Do not throw away any medicines via wastewater or household waste.

Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Repatha contains
- The active substance is evolocumab. Each cartridge contains 420 mg of evolocumab in 3.5 mL of solution (120 mg/mL).
- The other ingredients are proline, glacial acetic acid, polysorbate 80, sodium hydroxide, water for injections.

What Repatha looks like and contents of the pack

Repatha is a solution which is clear to opalescent, colourless to yellowish, and practically free from particles.

Each pack contains one single use cartridge co-packed with a single use automated mini-doser.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Manufacturer
Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Manufacturer
Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Амджен България ЕООД
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Slovenija
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Tel: +386 (0)1 585 1767

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Sverige
Amgen AB
Tel: +46 (0)8 6951100

United Kingdom (Northern Ireland)
Amgen Limited
Tel: +44 (0)1223 420305

This leaflet was last revised in.

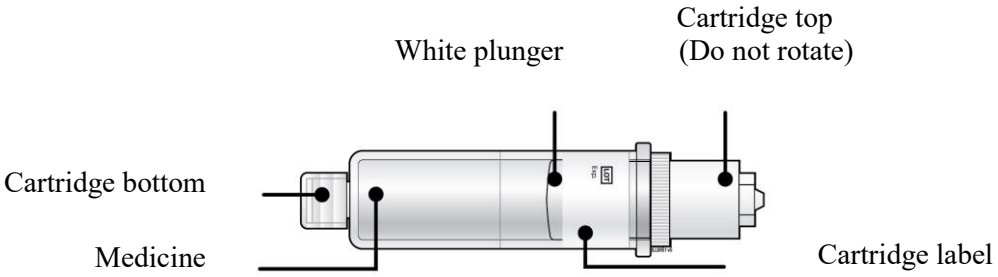
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions for use:
Repatha single use automated mini-doser and cartridge

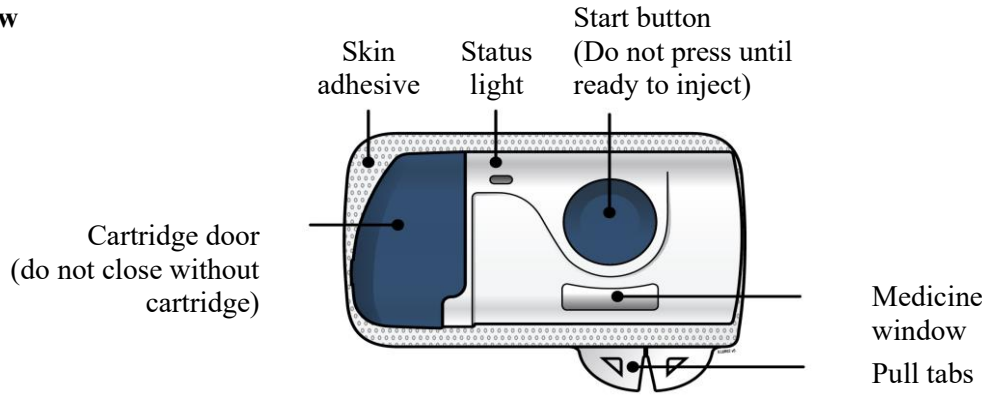
Guide to parts

Cartridge

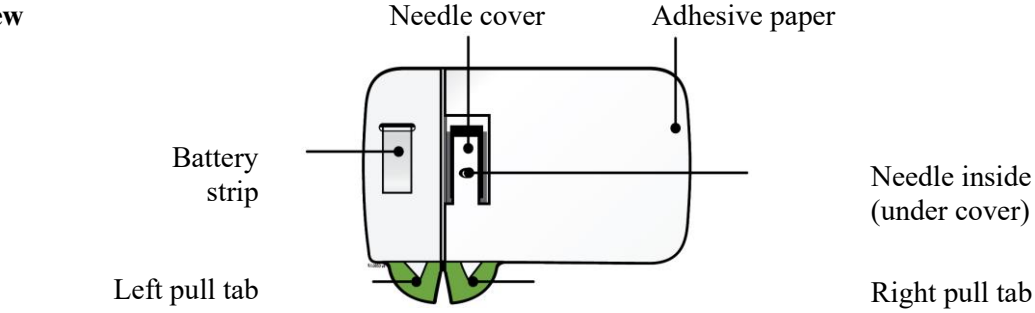


Automated mini-doser

Front view



Back view



Important: Needle is inside.

Important

Before you use the automated mini-doser and cartridge for use with Repatha, read this important information:

Storing your automated mini-doser and cartridge

- Keep the automated mini-doser and cartridge out of the sight and reach of children.
- **Do not** store the automated mini-doser and cartridge in extreme heat or cold. For example, avoid storing in your vehicle's glove box or boot. **Do not** freeze.

Using your automated mini-doser and cartridge

- **Do not** shake the automated mini-doser or cartridge.
- **Do not** remove the automated mini-doser and cartridge from the box or clear tray until you are ready to inject.
- **Do not** touch the start button until you place the loaded automated mini-doser and cartridge onto your skin and are ready to inject.
- Adult supervision is recommended for children age 13 years and younger while using the automated mini-doser and cartridge.
- You can only press the start button once. If an error occurs, the automated mini-doser cannot be used.
- **Do not** use the automated mini-doser and cartridge if either have been dropped onto a hard surface. Part of the automated mini-doser and cartridge may be broken even if you cannot see the break. Use a new automated mini-doser and cartridge.
- **Do not** reuse the automated mini-doser and cartridge. The automated mini-doser and cartridge are for single use only.
- **Do not** let the automated mini-doser get wet from water or any other liquids. It contains electronics that should not get wet.
- The single use automated mini-doser for subcutaneous injection is intended only for use with the cartridge.

In any above cases, use a new automated mini-doser and cartridge. A healthcare provider familiar with Repatha should be able to answer your questions.

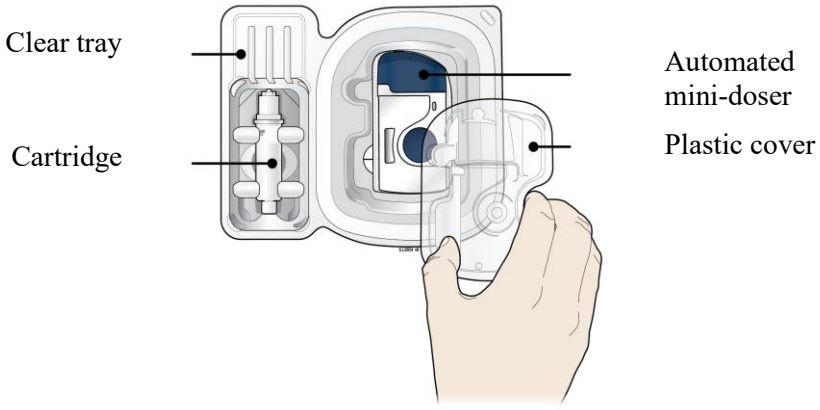
Step 1: Prepare	
A	**Remove the automated mini-doser and cartridge carton from the refrigerator. Wait 45 minutes.**

Important: Wait at least 45 minutes for the automated mini-doser and cartridge to naturally reach room temperature in the carton, before you inject.

- **Do not** try to warm the cartridge by using a heat source such as hot water or a microwave.
- **Do not** shake the automated mini-doser and cartridge.
- **Do not** use if any part of the cartridge appears cracked or broken.
- **Do not** use if the expiration date printed on the carton label has passed.

In any above cases, use a new automated mini-doser and cartridge.

B	**Open the carton and peel away the white paper cover. Remove the automated mini-doser cover from the clear tray.**



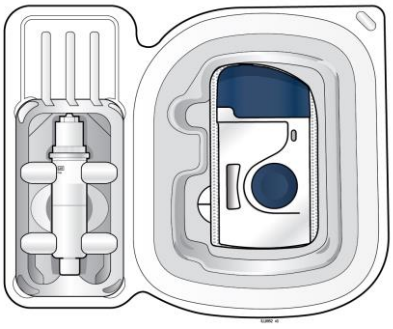
Leave the automated mini-doser and cartridge in the clear tray until you are ready to inject.

- **Do not** touch the start button until the automated mini-doser is on your skin and you are ready to inject.
- **Do not** use if the white paper cover is missing or damaged.

C	**Gather all materials needed for your injection and then wash your hands thoroughly with soap and water.**

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

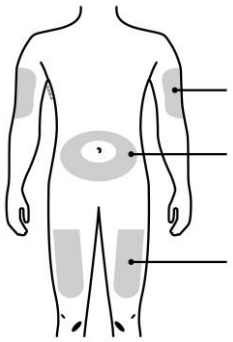
- Clear tray containing the automated mini-doser and cartridge
- Alcohol wipes
- Cotton ball or gauze pad
- Plaster
- Sharps disposal container



D	**Choose your automated mini-doser placement. Only use the outer arm if someone else is giving the injection.**

You can use:

- Your thigh
- Belly, except for a **2**-inch (**5** centimetre) area around your belly button
- Outer area of upper arm (only if someone else is giving the injection)



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

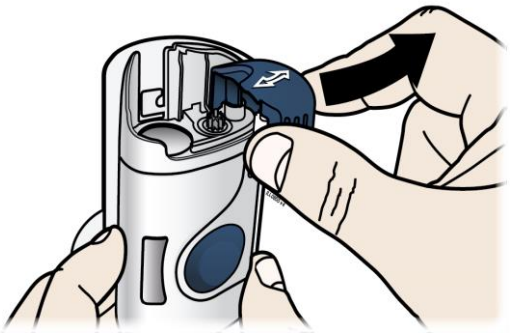
- **Do not** touch this area again before injecting.
- **Do not** inject into areas where the skin is tender, bruised, red or hard. Avoid injecting into areas with wrinkles, skin folds, scars, stretch marks, moles and excessive hair.

If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.

Important: To attach the automated mini-doser securely, it is important to use a firm and flat skin surface.

Step 2: Get ready	
E	**Open the automated mini-doser by swinging the cartridge door to the right. Then, leave the door open.**

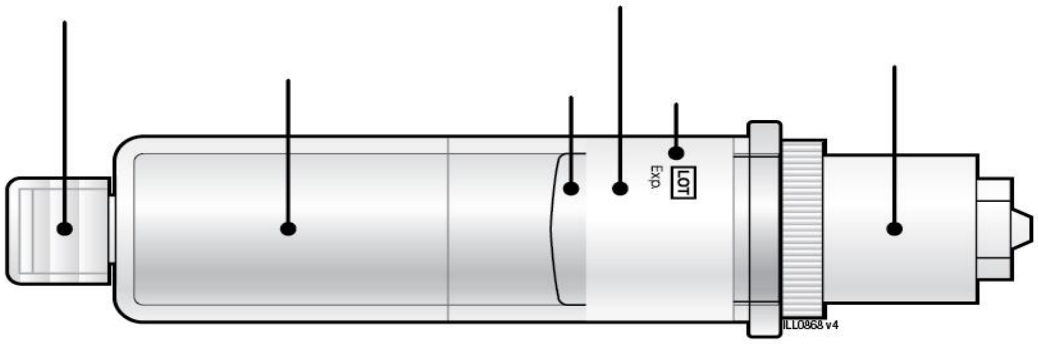
Do not press the start button until you are ready to inject.



F	**Inspect the cartridge.**

Cartridge label Cartridge top (do not rotate)

Cartridge bottom Medicine White plunger Expiration date

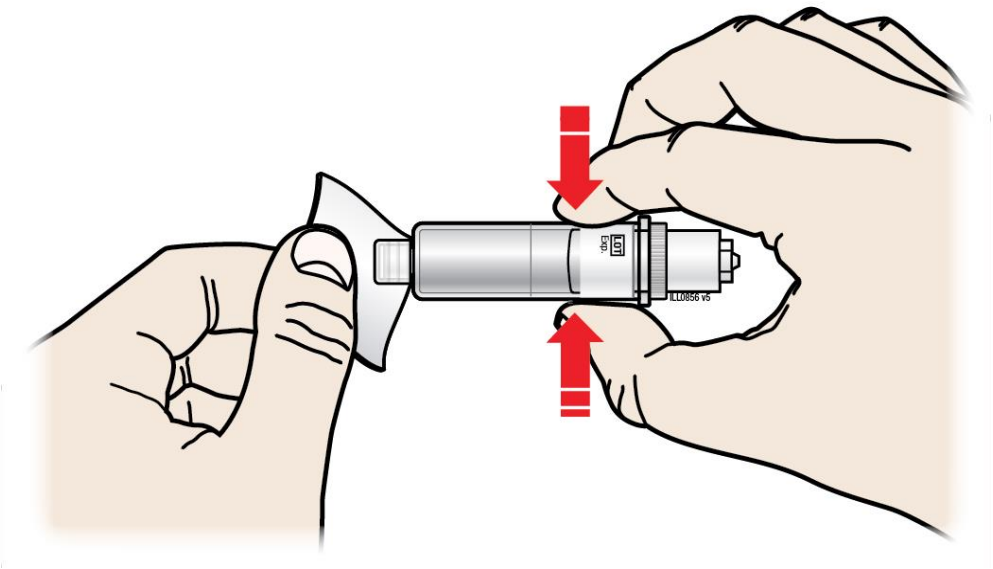


Make sure the medicine in the cartridge is clear and colourless to slightly yellow.

- **Do not** use if the medicine is cloudy or discoloured or contains flakes or particles.
- **Do not** use if any part of the cartridge appears cracked or broken.
- **Do not** use if pieces of the cartridge are missing or not securely attached.
- **Do not** use if the expiration date on the cartridge has passed.

In any above cases, use a new automated mini-doser and cartridge.

G	**Clean the cartridge bottom.**



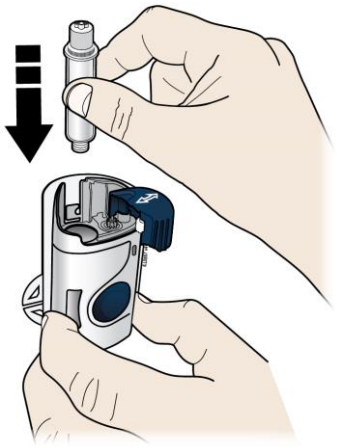
Grab here

With one hand, hold the cartridge barrel and clean the cartridge bottom with an alcohol wipe.

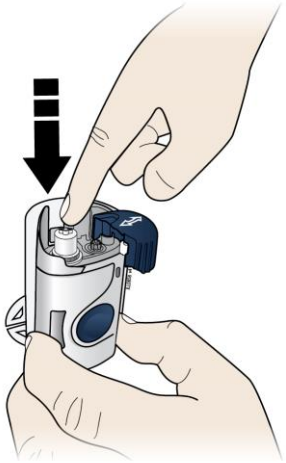
- **Do not** touch the bottom of the cartridge after cleaning with alcohol wipe.
- **Do not** remove or rotate the cartridge top or bottom.

H	**Load the cleaned cartridge into the automated mini-doser and firmly press on the top until it is secured in place.**

Load the cartridge **straight**



Press down **firmly**



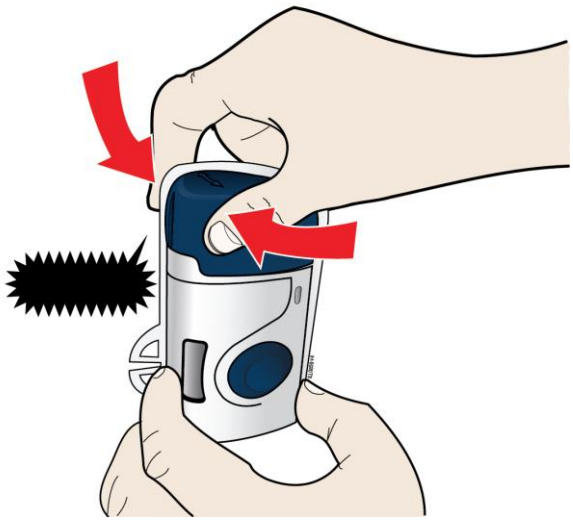
Insert the cartridge bottom first.

- **Do not** insert the cartridge more than 5 minutes before injection. This can dry out the medicine.
- **Do not** touch the start button until you have placed the loaded automated mini-doser on your skin.

I	**Swing the door to the left. Then, squeeze firmly until it snaps shut.**

Squeeze tight

snap

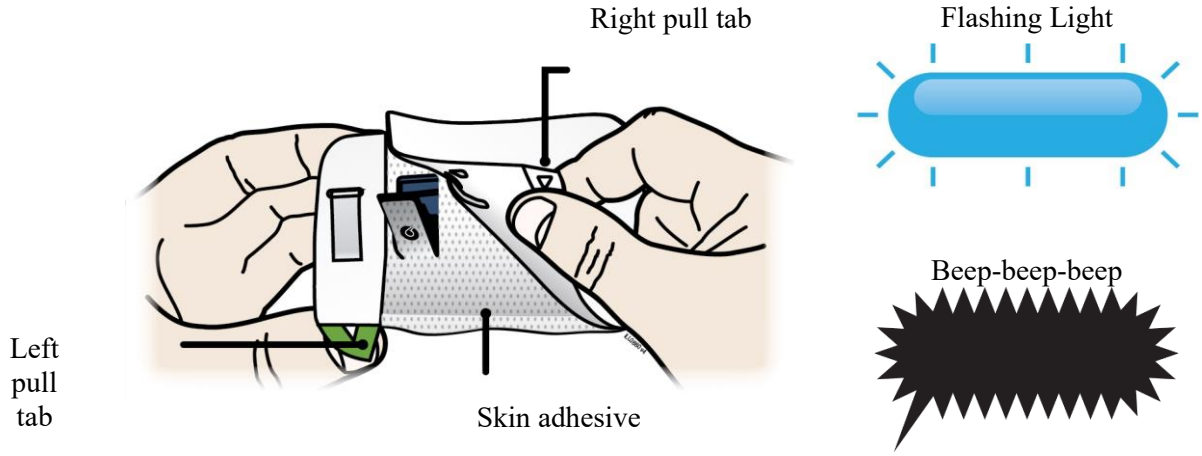


Make sure the cartridge fits securely in the automated mini-doser before you close the door.

- **Do not** close the door if the cartridge is missing or not fully inserted.
- **Do not** touch the start button until you have placed the loaded automated mini-doser on your skin.

Important: After you load the automated mini-doser, proceed to the next step without delay.

Step 3: Inject	
J	**Peel away both** green pull tabs to show the adhesive. The automated mini-doser is on when the blue status light flashes.

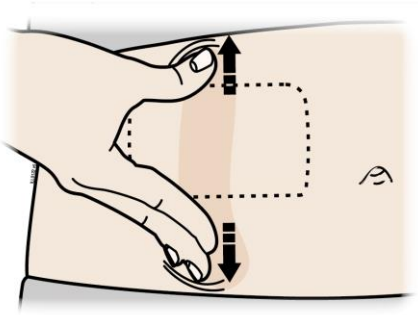


You must remove both green pull tabs to turn the loaded automated mini-doser on. You will hear beeping and see a flashing blue status light.

- **Do not** touch the skin adhesive.
- **Do not** touch the start button until you have placed the loaded automated mini-doser on your skin.
- **Do not** touch or contaminate the needle cover area.
- **Do not** place the loaded automated mini-doser on your body if the red status light flashes for more than 5 seconds.
- **Do not** pull the skin adhesive backing off of the automated mini-doser.
- **Do not** fold the skin adhesive over onto itself.

K	**To securely attach the automated mini-doser, prepare and clean an injection site that is less likely to have body hair, or you can trim the area. Use a firm and flat skin surface.**

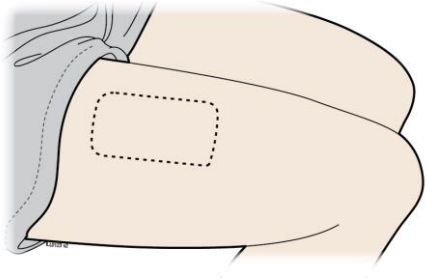
Belly area placement



Stretch method for belly

OR

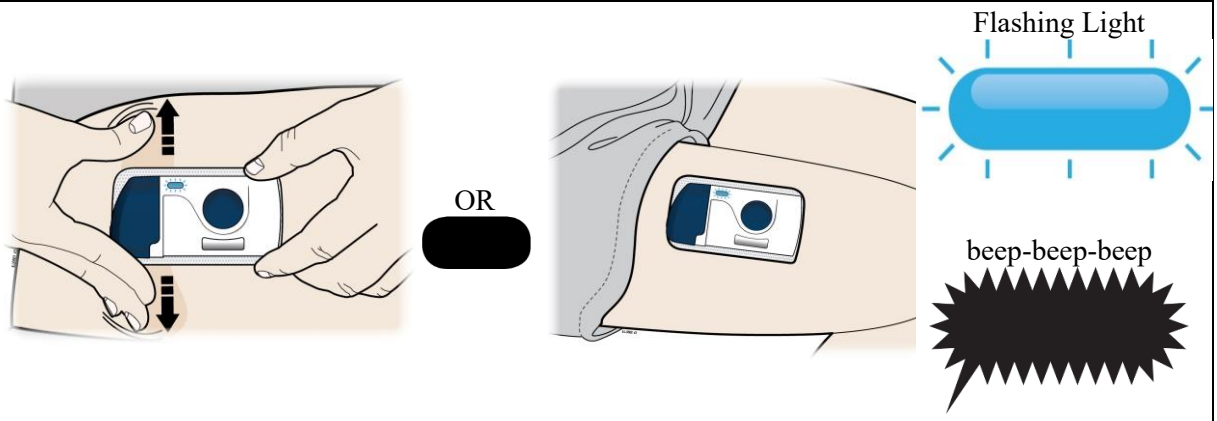
Thigh placement



Do not stretch for thigh

Important: Adjust your body posture to avoid skin folds and bulges.

L	When the blue light flashes, the automated mini-doser is ready. **Keep** the **stretch** (belly area method only). Hold the loaded automated mini-doser with the blue light visible, and place it on your skin. You may hear beeps.

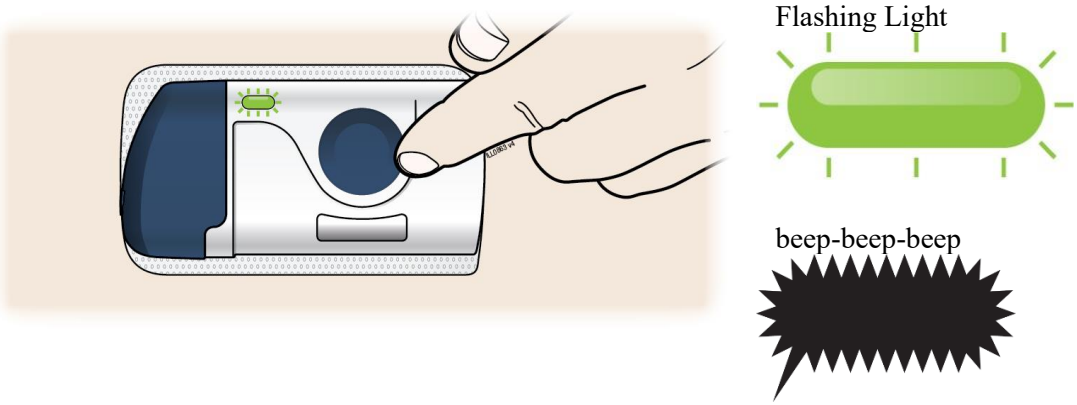


The loaded automated mini-doser will lay flat on your body. Make sure the entire adhesive is attached to your skin. Run a finger around the adhesive edges to secure it.

Make sure clothing does not get in the way of the loaded automated mini-doser, and you can see the blue light at all times.

- **Do not** try to reposition the loaded automated mini-doser after it has been placed onto your skin.

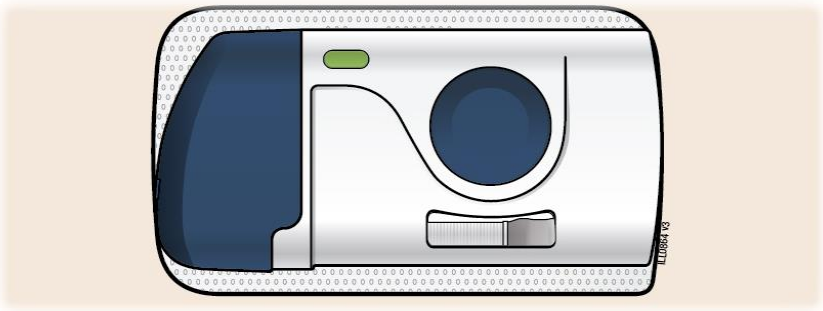
M	Firmly **press and release** the start button. A flashing green light and a click signals the injection has started.

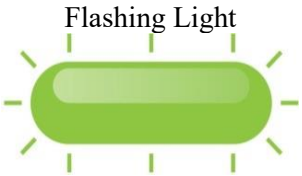


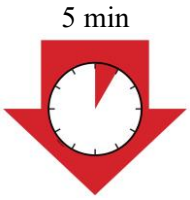
- You may hear a pumping sound.
- You may feel a needle pinch.
- Make sure you see a green, flashing status light.
- You may hear beeps indicating your injection has started.

Important: If medication leaks from the loaded automated mini-doser contact your doctor or pharmacist.

N	**Injection takes about 5 minutes. The status light turns solid green, and the device beeps, when done.**





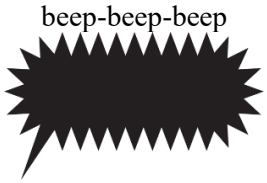


It is okay to hear a pumping sound start and stop during injection.

- Moderate physical activities can be performed during the injection process, such as walking, reaching and bending.

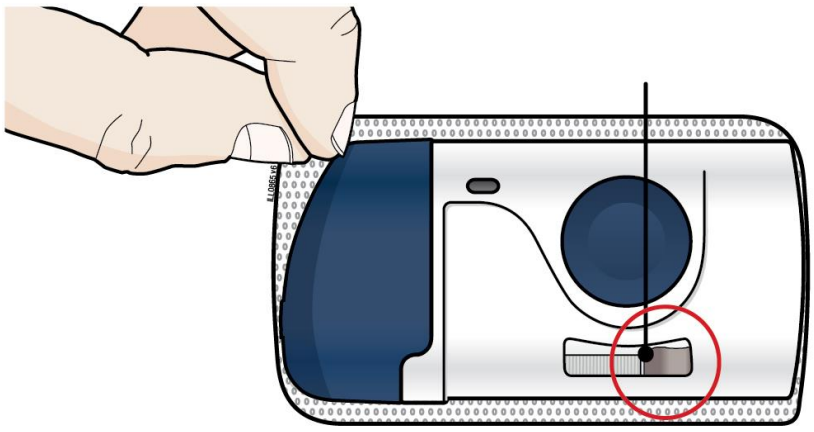
Injection is complete when:

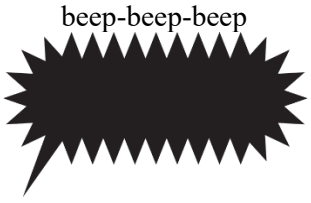
- The status light changes to solid green.
- You hear several beeps.



	Step 4: Finish
O	**When the injection is done, grab the skin adhesive to carefully peel the automated mini-doser off your skin. After removal, check the medicine window. The green light should now be off.**

Used plunger





Check to see that the used plunger completely fills the medicine window, and the green solid light turns off, letting you know all medicine has been injected. If the plunger did not fill the window, contact your doctor.

- The used automated mini-doser will beep when removed from your skin.
- It is normal to see a few drops of fluid on your skin after you remove the used automated mini-doser.

P	**Discard the used automated mini-doser in a sharps container.**

- The automated mini-doser contains batteries, electronics, and a needle.
- Put the used automated mini-doser in sharps disposal container right away after use. **Do not** throw away (dispose of) the automated mini-doser in your household waste.
- Talk with your healthcare provider about proper disposal. There may be local guidelines for disposal.
- **Do not** remove the used cartridge from the automated mini-doser.
- **Do not** reuse the automated mini-doser.
- **Do not** recycle the automated mini-doser or sharps disposal container or throw them into household waste.

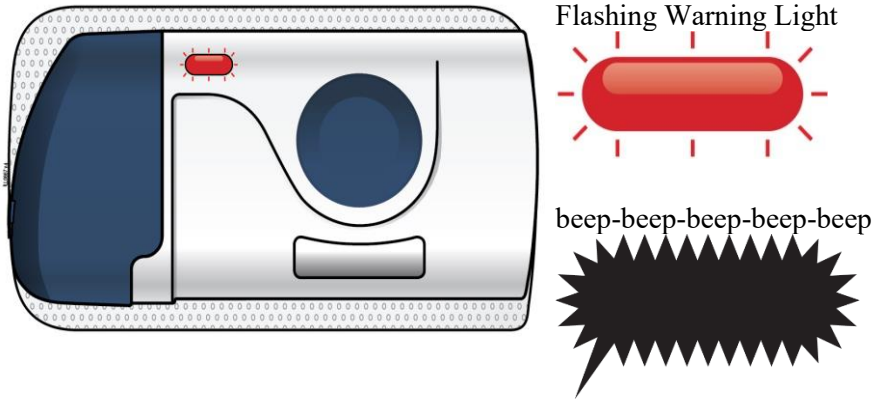
Important: Always keep the sharps disposal container out of the sight and reach of children.

Q	**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.

Troubleshooting

What to do if the loaded automated mini-doser status light continuously flashes red and you hear beeps.



Stop using the loaded automated mini-doser. If the automated mini-doser is attached to your body, carefully remove it.

Additional environmental conditions

Relative humidity range is 15% to 85%.
Altitude range is -300 metres to 3,500 metres (-984 feet to 11,483 feet).
During injection, keep the automated mini-doser a minimum of 30 cm (12 inches) away from other electronics such as mobile phones.
Warning: Do not modify the device.
Automated mini-doser operating temperature range is 15°C to 40°C.
www.devicepatents.com

SYMBOL TABLE					
					
Do not use if packaging is damaged	Keep dry	Refer to Instructions for Use	Type BF Applied Part	Single use	Sterilised using ethylene oxide

 0344

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