The content of this leaflet was approved by the Ministry of Health in January 2019 and updated according to the guidelines of the Ministry of Health in September 2019.

## 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

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection (injection).
Solution for injection (injection) (SureClick).

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hypercholesterolemia and mixed dyslipidemia

Repatha is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

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

Homozygous familial hypercholesterolemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia 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.

## 4.2 Posology and method of administration

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

Posology

*Primary hypercholesterolemia and mixed dyslipidemia in adults*
The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

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

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

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

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

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

*Pediatric population*
The safety and efficacy of Repatha in children aged less than 18 years has not been established in the indication for primary hypercholesterolemia and mixed dyslipidemia. No data are available.

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

Method of administration

Subcutaneous use.

Repatha is for subcutaneous injection into the abdomen, thigh or upper arm region. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard. Repatha 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 is intended for patient self-administration after proper training. Administration of Repatha can also be performed by an individual who has been trained to administer the product.

For single use only.

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

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Renal impairment

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

Hepatic impairment

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

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section 5.2). Repatha 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 allergic reactions.

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

Sodium content

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

## 4.5 Interaction with other medicinal products and other forms of interaction

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

The pharmacokinetic interaction between statins and evolocumab was evaluated in the Repatha clinical trials. An approximately 20% increase in the clearance of evolocumab was observed in patients

co-administered statins. This increased clearance is in part mediated by statins increasing the concentration of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with Repatha.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of 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 known influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

Adverse reactions reported in pivotal, controlled clinical studies, and spontaneous reporting, are displayed by system organ class and frequency in table 1 below using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

**Table 1. Adverse reactions with Repatha**

| MedDRA system organ class (SOC) | Adverse reactions | Frequency category |
|---|---|---|
| Infections and infestations | Influenza | Common |
| | Nasopharyngitis | Common |
| | Upper respiratory tract infection | Common |
| Immune system disorders | Rash | Common |
| | Urticaria | Uncommon |
| Gastrointestinal disorders | Nausea | Common |
| Skin and subcutaneous tissue disorders | Angioedema | Rare |
| Musculoskeletal and connective tissue disorders | Back pain | Common |
| | Arthralgia | Common |
| General disorders and administration site conditions | Injection site reactions[1] | Common |

[1] See section Description of selected adverse reactions

Description of selected adverse reactions

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

Pediatric population

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

The safety and effectiveness of Repatha in pediatric patients with primary hypercholesterolemia and mixed dyslipidemia has not been established.

Elderly population

Of the 18,546 patients treated with Repatha in double-blind clinical studies 7,656 (41.3%) were ≥ 65 years old, while 1,500 (8.1%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

Immunogenicity

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

## 4.9 Overdose

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

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents. ATC code: C10AX13

Mechanism of action

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

Pharmacodynamic effects

In clinical trials, Repatha reduced unbound PCSK9, LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and increased HDL-C and ApoA1 in patients with primary hypercholesterolemia and mixed dyslipidemia.

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

Subcutaneous regimens of 140 mg every 2 weeks and 420 mg once monthly were equivalent in average LDL-C lowering (mean of weeks 10 and 12) resulting in -72 to -57% from baseline compared with placebo. Treatment with Repatha resulted in a similar reduction of LDL-C when used alone or in combination with other lipid-lowering therapy.

Clinical efficacy in primary hypercholesterolemia and mixed dyslipidemia

LDL-C reduction of approximately 55% to 75% was achieved with Repatha as early as week 1 and maintained during long-term therapy. Maximal response was generally achieved within 1 to 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly. Repatha was effective in all subgroups relative to placebo and ezetimibe, with no notable differences observed between subgroups, such as age, race, gender, region, body-mass index, National Cholesterol Education Program risk, current smoking status, baseline coronary heart disease (CHD) risk factors, family history of premature CHD, glucose tolerance status, (i.e. diabetes mellitus type 2, metabolic syndrome, or neither), hypertension, statin dose and intensity, unbound baseline PCSK9, baseline LDL-C and baseline TG.

In 80-85% of all primary hyperlipidemia patients treated with either dose, Repatha 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 Repatha achieved an LDL-C of < 2.6 mmol/L and up to 95% achieved an LDL-C < 1.8 mmol/L at the mean of weeks 10 and 12.

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

LAPLACE-2 was an international, multicenter, double-blind, randomized, 12-week study in 1,896 patients with primary hypercholesterolemia or mixed dyslipidemia who were randomized to receive Repatha in combination with statins (rosuvastatin, simvastatin or atorvastatin). Repatha 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, multicenter, double-blind, randomized, placebo-controlled, 12-week study in 329 patients with heterozygous familial hypercholesterolemia 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 Repatha compared with placebo in patients with primary hypercholesterolemia and mixed dyslipidemia - mean percent change from baseline to average of weeks 10 and 12 (%, 95% CI)**

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

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

Statin-intolerant patients

GAUSS-2 was an international, multicenter, double-blind, randomized, ezetimibe-controlled, 12-week study in 307 patients who were statin-intolerant or unable to tolerate an effective dose of a statin. 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, multicenter, double-blind, randomized, placebo and ezetimibe-controlled, 12-week study of Repatha in 614 patients with primary hypercholesterolemia and mixed dyslipidemia. 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 Repatha compared with ezetimibe in patients with primary hypercholesterolemia and mixed dyslipidemia - mean percent change from baseline to average of weeks 10 and 12 (%, 95% CI)**

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

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

Long-term efficacy in primary hypercholesterolemia and mixed dyslipidemia

DESCARTES was an international, multicenter, double-blind, randomized, placebo-controlled, 52-week study in 901 patients with hyperlipidemia who received diet alone, atorvastatin, or a combination of atorvastatin and ezetimibe. 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 optimized 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 Repatha compared with placebo in patients with primary hypercholesterolemia and mixed dyslipidemia - mean percent change from baseline to week 52 (%, 95% CI)**

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

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

OSLER and OSLER-2 were two randomized, 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 randomized 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 multicenter, 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 hypercholesterolemia (FH), including homozygous familial hypercholesterolemia. A total of 194 severe familial hypercholesterolemia (non-HoFH) patients and 106 homozygous familial hypercholesterolemia patients enrolled in TAUSSIG. All patients in the study were initially treated with 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 hypercholesterolemia (non-HoFH) (see table 5).

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

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

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

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

The long-term safety of sustained very low levels of LDL-C (i.e. < 0.65 mmol/L [< 25 mg/dL]) has not yet been established. Available data demonstrate that there are no clinically meaningful differences between the safety profiles of patients with LDL-C levels < 0.65 mmol/L and those with higher LDL-C, see section 4.8.

Treatment of homozygous familial hypercholesterolemia

TESLA was an international, multicenter, double-blind, randomized, placebo-controlled 12-week study in 49 homozygous familial hypercholesterolemia patients aged 12 to 65 years. 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 6). 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 hypercholesterolemia.

**Table 6. Treatment effects of Repatha compared with placebo in patients with homozygous familial hypercholesterolemia - mean percent change from baseline to week 12 (%, 95% CI)**

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

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

Long-term efficacy in homozygous familial hypercholesterolemia

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 hypercholesterolemia not on apheresis and approximately 10% to 30% in patients with homozygous familial hypercholesterolemia on apheresis (see table 7). Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of long-term Repatha administration in patients with homozygous familial hypercholesterolemia. Reductions in LDL-C and changes in other lipid parameters in 14 adolescent patients (aged ≥ 12 to < 18 years) with homozygous familial hypercholesterolemia are comparable to those in the overall population of patients with homozygous familial hypercholesterolemia.

**Table 7. Effect of Repatha on LDL-C in patients with homozygous familial hypercholesterolemia - mean percent change from baseline to OLE week 216 (and associated 95% CI)**

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

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

Cardiovascular risk reduction in adults with established atherosclerotic cardiovascular disease

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

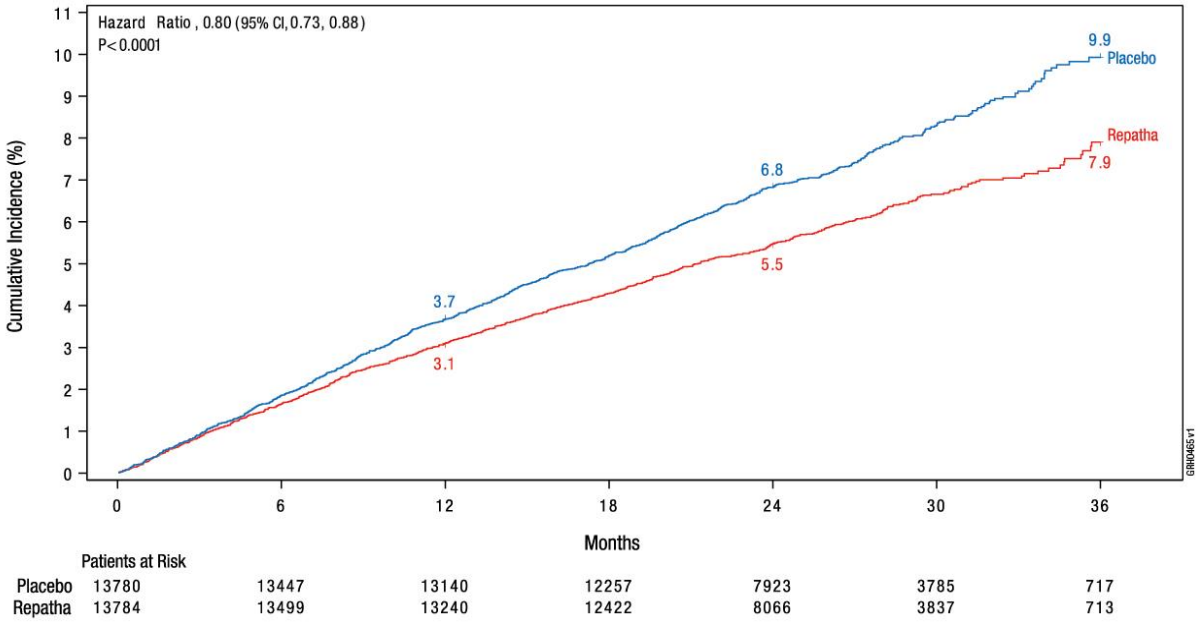
Repatha significantly reduced the risk of cardiovascular events defined as the composite of time to first CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina (see table 8); the Kaplan-Meier curves for the primary and key secondary composite endpoints separated at 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 revascularization; no significant difference was seen on cardiovascular or all-cause mortality however the study was not designed to detect such a difference.

**Table 8. Effect of Repatha on major cardiovascular events**

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

[a] Based on a Cox model stratified by the randomization stratification factors collected via IVRS.
[b] 2-sided log-rank test stratified by randomization stratification factors collected via IVRS.
[c] Nominal significance.
[d] The treatment effect on stroke was driven by a reduction in risk of ischemic stroke; there was no effect on hemorrhagic or undetermined stroke.
[e] Assessment of time to hospitalization for unstable angina was ad-hoc.

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




## 5.2 Pharmacokinetic properties

Absorption and distribution

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

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

Biotransformation

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

Elimination

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

In patients with primary hypercholesterolemia or mixed dyslipidemia 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 hypercholesterolemic patients (non-familial hypercholesterolemia or familial hypercholesterolemia) taking concomitant statins.

Linearity/non-linearity

Following a single 420 mg intravenous dose, the mean (SD) systemic clearance was estimated to be 12 (2) mL/hr. In clinical studies with repeated subcutaneous dosing over 12 weeks, dose proportional increases in exposure were observed with dose regimens of 140 mg and greater. An approximate two to three-fold accumulation was observed in trough serum concentrations ($C_{min}$ (SD) 7.21 (6.6)) following 140 mg doses every 2 weeks or following 420 mg doses administered monthly ($C_{min}$ (SD) 11.2 (10.8)), and serum trough concentrations approached steady-state by 12 weeks of dosing.

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

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from the Repatha clinical trials did not reveal a difference in pharmacokinetics of evolocumab in patients with mild or moderate renal impairment relative to non-renally impaired patients. There is limited experience with Repatha in patients with severe renal impairment (see section 4.4).

Hepatic impairment

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

Body weight

Body weight was a significant covariate in population PK analysis impacting evolocumab trough concentrations, however there was no impact on LDL-C reduction. Following repeat subcutaneous administration of 140 mg every 2 weeks, the 12-week trough concentrations were 147% higher and 70% lower in patients of 69 kg and 93 kg respectively, than that of the typical 81 kg subject. Less impact from body weight was seen with repeated subcutaneous evolocumab 420 mg monthly doses.

Other special populations

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

## 5.3 Preclinical safety data

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

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

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

Apart from a reduced T-cell Dependent Antibody Response in cynomolgus monkeys immunized with keyhole limpet hemocyanin (KLH) after 3 months of treatment with evolocumab, no adverse effects were

observed in hamsters (up to 3 months) and cynomolgus monkeys (up to 6 months) at exposures much higher than patients receiving evolocumab at 420 mg once monthly. The intended pharmacological effect of decreased serum LDL-C and total cholesterol were observed in these studies and was reversible upon cessation of treatment.

In combination with rosuvastatin for 3 months, no adverse effects were observed in cynomolgus monkeys at exposures much higher than patients receiving 420 mg evolocumab once monthly. Reductions in serum LDL-C and total cholesterol were more pronounced than observed previously with evolocumab alone, and were reversible upon cessation of treatment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

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

### 6.2 Incompatibilities

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

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

### 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
Keep in the original carton in order to protect from light.

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

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 30 days.

### 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.

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

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

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

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

## 7. MARKETING AUTHORIZATION HOLDER

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

## 8. REGISTRATION HOLDER

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