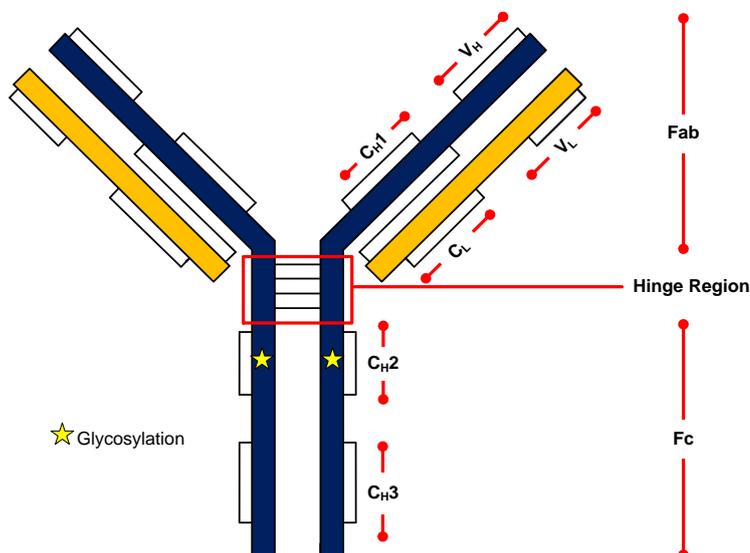


## Repatha® (evolocumab)

### NAME OF THE MEDICINE

Repatha is the Amgen Inc. trademark for evolocumab (rch)

**Figure 1. Schematic of Repatha Structure**



V<sub>H</sub> is the variable domain of the heavy chain  
 C<sub>H</sub>1, C<sub>H</sub>2, and C<sub>H</sub>3 are the constant domains of the heavy chain  
 V<sub>L</sub> is the variable domain of the light chain  
 C<sub>L</sub> is the constant domain of the light chain

### DESCRIPTION

Repatha is a fully human immunoglobulin G2 (IgG2) monoclonal antibody with high affinity binding to Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). Repatha has an approximate molecular weight of 144 kDa and is produced using recombinant DNA technology in mammalian (Chinese Hamster Ovary, CHO) cells.

Repatha is a sterile, preservative-free solution, clear to opalescent; colourless to yellowish solution for injection, practically free from particles. Repatha is formulated from proline, glacial acetic acid, polysorbate 80, water for injection and sodium hydroxide.

### PHARMACOLOGY

#### **Mechanism of action**

Repatha binds selectively and with high affinity to PCSK9 and inhibits 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 low density lipoprotein-cholesterol (LDL-C).

### **Pharmacodynamics**

Clinical studies have demonstrated that elevated levels of total cholesterol (TC), non-high density lipoprotein cholesterol (non-HDL-C), LDL-C and apolipoprotein B (ApoB), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of TC, non-HDL-C, LDL-C, ApoB and lipoprotein(a) [Lp(a)], and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) or Lp(a) on the risk of cardiovascular morbidity and mortality has not been determined.

In clinical trials, in patients with primary hypercholesterolaemia [Heterozygous familial hypercholesterolaemia (HeFH) and atherosclerotic cardiovascular disease (CVD)], Repatha reduced LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), VLDL-C, TG and Lp(a), and increased HDL-C and ApoA1.

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.

Based on dose-range finding studies, subcutaneous regimens of 140 mg every 2 weeks and 420 mg once monthly were identified as the optimal regimens to achieve maximal LDL-C lowering (Figure 2) and were equivalent in average LDL-C lowering (mean of weeks 10 and 12), resulting in -72 to -57% from baseline compared to placebo.

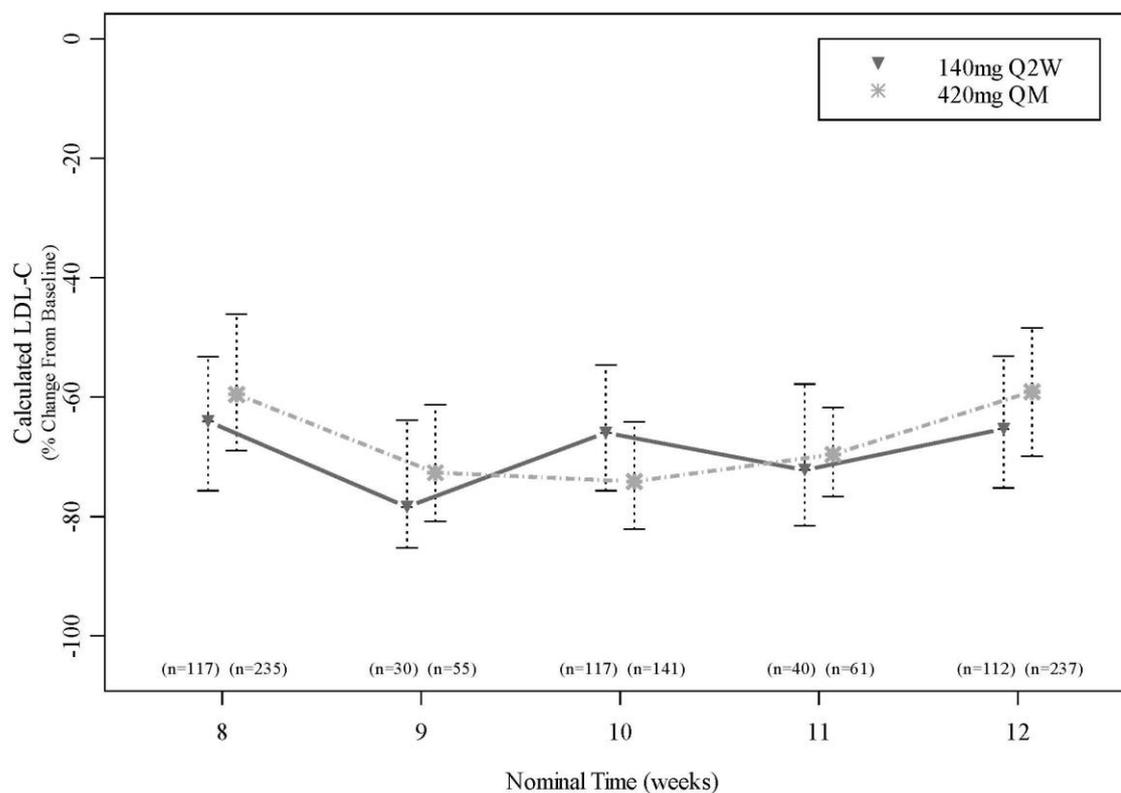
Treatment with Repatha resulted in similar reduction of LDL-C when used alone or in combination with other lipid lowering therapy. The effect of LDL-C lowering is sustained; the longest duration measured was 112 weeks.

Doses of 140 mg subcutaneously every 2 weeks and 420 mg subcutaneously once monthly achieve approximately 80% of the theoretical maximal reduction in calculated LDL-C at the mean of weeks 10 and 12 based on exposure response models. Intrinsic and extrinsic covariates, such as demographics, co-medications, laboratory variables

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and disease states are not expected to modify LDL-C response (see **DOSAGE AND ADMINISTRATION**).

**Figure 2. Effect of subcutaneous administration of Repatha 140 mg every 2 weeks or 420 mg once monthly on LDL-C**



Vertical lines represent median values of calculated LDL-C with 25th and 75th percentiles.

### **Pharmacokinetics**

Evolocumab exhibits non-linear kinetics as a result of binding to PCSK9. Administration of the 140 mg dose in healthy volunteers resulted in a  $C_{max}$  mean (standard deviation [SD]) of 18.6 (7.3)  $\mu\text{g/mL}$  and  $AUC_{last}$  mean (SD) of 188 (98.6)  $\text{day}\cdot\mu\text{g/mL}$ . Administration of the 420 mg dose in healthy volunteers resulted in a  $C_{max}$  mean (SD) of 59.0 (17.2)  $\mu\text{g/mL}$  and  $AUC_{last}$  mean (SD) of 924 (346)  $\text{day}\cdot\mu\text{g/mL}$ . Following a single 420 mg intravenous dose, the mean (SD) systemic clearance was estimated to be 12 (2)  $\text{mL/hr}$ . An approximate 2- to 3-fold accumulation was observed in trough serum concentrations ( $C_{min}$  [SD] 7.21 [6.6]) following 140 mg doses administered subcutaneously every 2 weeks or following 420 mg doses administered subcutaneously monthly ( $C_{min}$  [SD] 11.2

[10.8]), and serum trough concentrations approached steady state by 12 weeks of dosing.

### **Absorption**

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 and estimated absolute bioavailability was 72%.

### **Distribution**

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

### **Metabolism**

As a fully human IgG2 antibody, the clearance of Repatha is mediated by specific binding and complex formation with its target ligand, PCSK9, as well as by typical IgG clearance processes in the reticuloendothelial system (RES). Repatha is expected to be degraded into small peptides and amino acids via these catabolic pathways.

### **Excretion**

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

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

An approximate 20% increase in the clearance of Repatha was observed in patients co-administered with statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9 which did not adversely impact the pharmacodynamic effect of Repatha on lipids. Population pharmacokinetic analysis indicated no appreciable differences in evolocumab serum concentrations in hypercholesterolaemic patients (non-FH or FH) taking concomitant statins (see **INTERACTIONS WITH OTHER MEDICINES**).

### **Special populations**

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

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### *Hepatic impairment*

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% to 50% lower compared with 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 subjects. This resulted in similar time course and extent of absolute LDL-C lowering.

### *Renal impairment*

Population pharmacokinetic analysis of integrated data from the Repatha clinical trials did not reveal a difference in pharmacokinetics in CKD patients with stages 2 and 3 renal impairment relative to non-renally impaired patients.

## **CLINICAL TRIALS**

### **Summary of clinical efficacy**

#### **Primary hypercholesterolaemia:**

- Repatha reduced 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.
  - Repatha was superior to ezetimibe in reducing LDL-C, total cholesterol, ApoB, non-HDL-C, Lp(a), TC/HDL-C, and ApoB/ApoA1.
  - Repatha 140 mg every 2 weeks and 420 mg once monthly dosing regimens are clinically equivalent.
  - LDL-C reduction of approximately 55% to 75% was achieved with Repatha as early as week 1 and maintained with long term therapy. Maximal response was generally achieved within 1 to 2 weeks after dosing.
  - In 80-85% of all 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% patients treated with either dose of Repatha achieved an LDL-C  $< 1.8$  mmol/L at the mean of weeks 10 and 12.
  - Repatha was effective in reducing LDL-C regardless of baseline characteristics, with no notable differences observed between subgroup, such as age, race,
-

gender, region, body mass index, National Cholesterol Education Program (NCEP) 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.

#### **Homozygous familial hypercholesterolaemia:**

- Repatha was effective in reducing LDL-C, TC, ApoB, and non-HDL-C in patients with homozygous familial hypercholesterolaemia (HoFH).
- Repatha 420 mg once monthly and 420 mg once every 2 weeks demonstrated a sustained treatment effect as evidenced by reduction in LDL-C of approximately 20% to 30% in patients with HoFH not on apheresis and approximately 15% to 25% in patients with HoFH on apheresis.
- No overall differences in safety or efficacy of Repatha were observed between adolescent and adult patients with HoFH.

#### **Clinical trials for primary hypercholesterolaemia**

##### **Combination with statin or statin with other lipid lowering therapies**

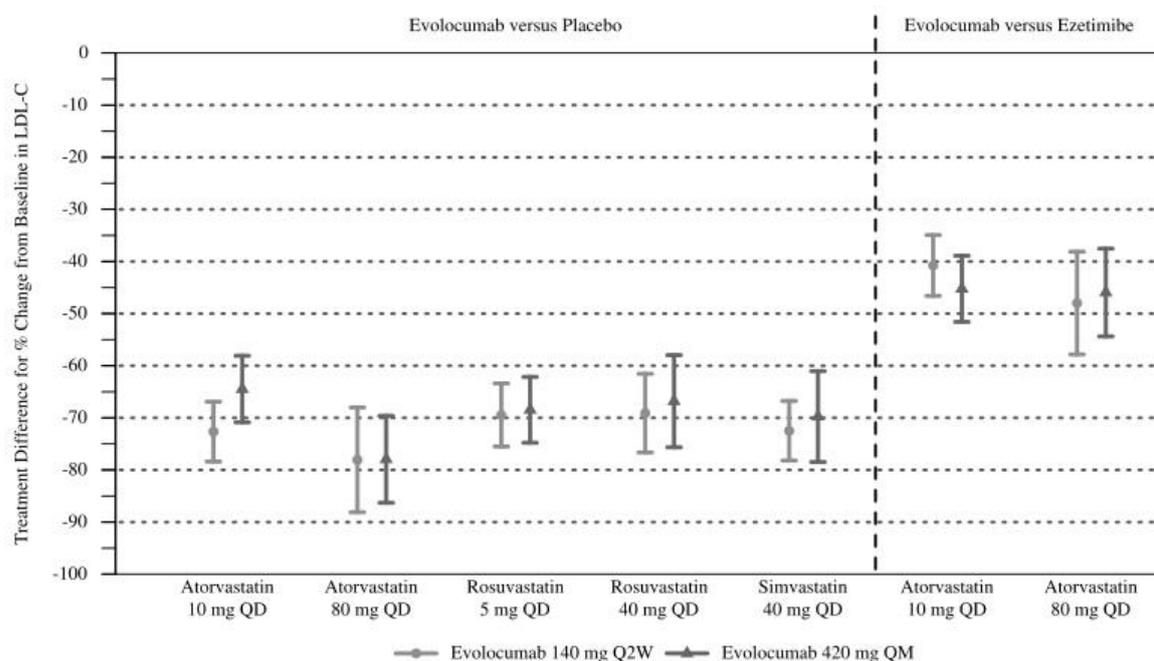
LAPLACE-2 was an international, multicentre, double-blind, randomised, 12-week study of Repatha in 1896 patients with primary hypercholesterolaemia who were randomised to receive Repatha in combination with statins (rosuvastatin, simvastatin or atorvastatin). Repatha was compared with placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group.

In LAPLACE-2, Repatha exhibited consistent treatment effects of lowering LDL-C and improving other lipid parameters across all statins and statin doses that were evaluated.

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 to placebo and ezetimibe for the atorvastatin group ( $p < 0.001$ ) (Figure 3). 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 with 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 ( $p < 0.001$ ).

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**Figure 3. Effect of Repatha on LDL-C when combined with statins – mean LDL-C percent change from baseline of weeks 10 and 12\***



\*All differences compared with placebo and ezetimibe are statistically significant ( $p < 0.001$ ). Vertical lines represent the 95% confidence interval around the mean differences of Repatha compared with control.

In a pre-specified analysis of LAPLACE-2, Repatha significantly reduced LDL-C, 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 with placebo for the combined rosuvastatin, simvastatin and atorvastatin groups ( $p < 0.001$ ) (Table 1).

Consistent treatment effects were observed in an analysis of Repatha compared with ezetimibe for the combined atorvastatin treatment groups (Table 2).

RUTHERFORD-2 was an international, multicentre, double-blind, randomised, placebo-controlled, 12-week study of Repatha in 329 patients with heterozygous familial hypercholesterolaemia (HeFH) 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 with placebo ( $p < 0.05$ ) (Table 1).

**Table 1. Treatment effects of Repatha compared with placebo in patients with primary hypercholesterolaemia - 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 (Combined rosuvastatin, simvastatin, & atorvastatin groups)	140 mg Q2W (N=555)	-72 <sup>b</sup> (-75, -69)	-60 <sup>b</sup> (-63, -58)	-56 <sup>b</sup> (-58, -53)	-41 <sup>b</sup> (-43, -39)	-30 <sup>b</sup> (-35, -25)	-18 <sup>b</sup> (-23, -14)	6 <sup>b</sup> (4, 8)	-17 <sup>b</sup> (-22, -13)	3 <sup>b</sup> (1, 5)	-45 <sup>b</sup> (-47, -42)	-56 <sup>b</sup> (-59, -53)
	420 mg QM (N=562)	-69 <sup>b</sup> (-73, -65)	-60 <sup>b</sup> (-63, -57)	-56 <sup>b</sup> (-58, -53)	-40 <sup>b</sup> (-42, -37)	-27 <sup>b</sup> (-31, -24)	-22 <sup>b</sup> (-28, -17)	8 <sup>b</sup> (6, 10)	-23 <sup>b</sup> (-28, -17)	5 <sup>b</sup> (3, 7)	-46 <sup>b</sup> (-48, -43)	-58 <sup>b</sup> (-60, -55)
RUTHERFORD 2 (HeFH)	140 mg Q2W (N=110)	-61 <sup>b</sup> (-67, -55)	-56 <sup>b</sup> (-61, -51)	-49 <sup>b</sup> (-54, -44)	-42 <sup>b</sup> (-46, -38)	-31 <sup>b</sup> (-38, -24)	-23 <sup>b</sup> (-29, -16)	8 <sup>b</sup> (4, 12)	-22 <sup>b</sup> (-29, -15)	7 <sup>a</sup> (3, 12)	-47 <sup>b</sup> (-51, -42)	-53 <sup>b</sup> (-58, -48)
	420 mg QM (N=110)	-66 <sup>b</sup> (-72, -61)	-60 <sup>b</sup> (-65, -55)	-55 <sup>b</sup> (-60, -50)	-44 <sup>b</sup> (-48, -40)	-31 <sup>b</sup> (-38, -24)	-16 <sup>b</sup> (-23, -8)	9 <sup>b</sup> (5, 14)	-17 <sup>b</sup> (-24, -9)	5 <sup>a</sup> (1, 9)	-49 <sup>b</sup> (-54, -44)	-56 <sup>b</sup> (-61, -50)

Key: Q2W = once every 2 weeks, QM = once monthly, HeFH = Heterozygous familial hypercholesterolaemia; <sup>a</sup> p value < 0.05 when compared with placebo. <sup>b</sup> p value < 0.001 when compared with placebo.

**Statin-intolerant therapy**

GAUSS-2 was an international, multicentre, double-blind, randomised, ezetimibe-controlled, 12-week study of Repatha in 307 patients who were statin-intolerant or unable to tolerate an effective dose of a statin. Repatha significantly reduced LDL-C compared to 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 ezetimibe (p<0.001) (Table 2).

**Table 2. Treatment effects of Repatha compared with ezetimibe in patients with primary hypercholesterolaemia– 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 (combined atorvastatin groups)	140 mg Q2W (N=219)	-43 (-50, -37)	-34 (-39, -30)	-34 (-38, -30)	-23 (-26, -19)	-30 (-35, -25)	-1 (-7, 5)	7 (4, 10)	-2 (-9, 5)	7 (4, 9)	-27 (-30, -23)	-38 (-42, -34)
	420 mg QM (N=220)	-46 (-51, -40)	-39 (-43, -34)	-40 (-44, -36)	-25 (-29, -22)	-33 (-41, -26)	-7 (-20, 6)	8 (5, 12)	-8 (-21, 5)	7 (2, 11)	-30 (-34, -26)	-42 (-47, -38)
GAUSS-2 (Statin intolerant)	140 mg Q2W (N=103)	-38 <sup>b</sup> (-44, -33)	-32 <sup>b</sup> (-36, -27)	-32 <sup>b</sup> (-37, -27)	-24 <sup>b</sup> (-28, -20)	-24 <sup>b</sup> (-31, -17)	-2 (-10, 7)	5 (1, 10)	-3 (-11, 6)	5 <sup>a</sup> (2, 9)	-27 <sup>b</sup> (-32, -23)	-35 <sup>b</sup> (-40, -30)
	420 mg QM (N=102)	-39 <sup>b</sup> (-44, -35)	-35 <sup>b</sup> (-39, -31)	-35 <sup>b</sup> (-40, -30)	-26 <sup>b</sup> (-30, -23)	-25 <sup>b</sup> (-34, -17)	-4 (-13, 6)	6 (1, 10)	-6 (-17, 4)	3 (-1, 7)	-30 <sup>b</sup> (-35, -25)	-36 <sup>b</sup> (-42, -31)

Key: Q2W = once every 2 weeks, QM = once monthly <sup>a</sup> p value <0.05 when compared with ezetimibe; <sup>b</sup> p value <0.001 when compared with ezetimibe.

### Long-term efficacy in primary hypercholesterolaemia

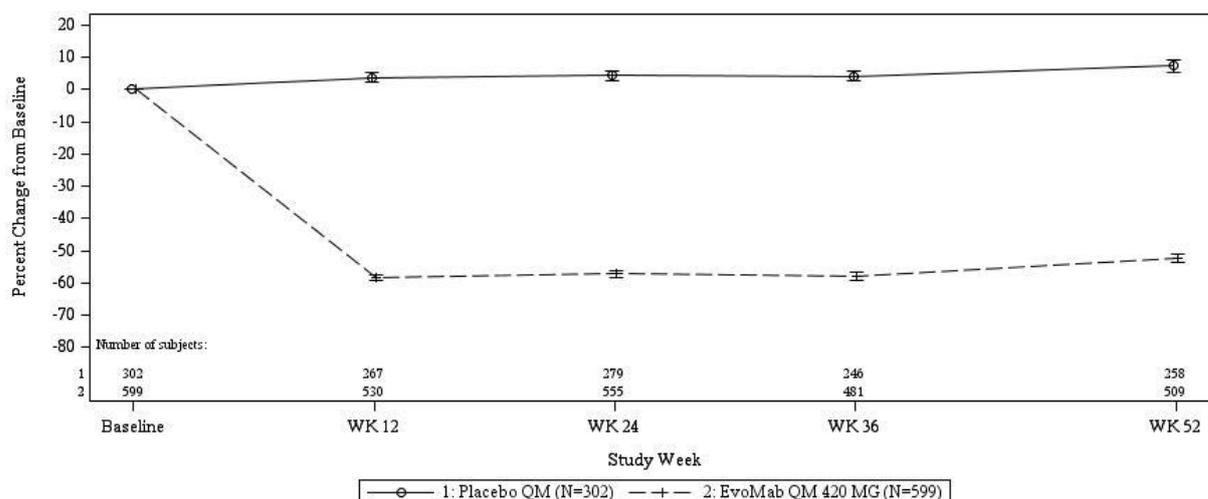
DESCARTES was an international, multicentre, double-blind, randomised, placebo-controlled, 52-week study of Repatha in 901 patients with hypercholesterolaemia who were receiving diet alone, atorvastatin, or a combination of atorvastatin and ezetimibe. Repatha 420 mg once monthly significantly reduced 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 (Figure 4). 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 420 mg once monthly significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG, and Lp(a), and increased HDL-C at week 52 compared with placebo ( $p < 0.001$ ) (Table 3).

**Table 3. Treatment effects of Repatha compared with placebo in patients with primary hypercholesterolaemia– 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 <sup>b</sup> (-64, -55)	-50 <sup>b</sup> (-54, -46)	-44 <sup>b</sup> (-48, -41)	-33 <sup>b</sup> (-36, -31)	-22 <sup>b</sup> (-26, -19)	-29 <sup>b</sup> (-40, -18)	5 <sup>b</sup> (3, 8)	-12 <sup>b</sup> (-17, -6)	3 (1, 5)	-37 <sup>b</sup> (-40, -34)	-46 <sup>b</sup> (-50, -43)

Key: QM = once monthly <sup>b</sup> p value <0.001 when compared with placebo.

**Figure 4. Mean percent change from baseline in calculated LDL-C by scheduled visit and investigational product (DESCARTES)**



DESCARTES - Full Analysis Set.

N = number of subjects randomised and dosed in the full analysis set;

EvoMab = Repatha; WK = week; QM = once monthly (subcutaneous); MG = milligrams.

Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

### **Ongoing studies**

OSLER 1 and OSLER 2 are two ongoing, 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-1 and week 48 in OSLER-2), patients were eligible to enter the all Repatha period in which all patients could receive open-label Repatha for either another 4 years (OSLER-1) or 1 year (OSLER-2).

A total of 1324 patients enrolled in OSLER-1. Repatha 420 mg once monthly reduced LDL-C from baseline at week 12 and week 52 compared with control. Treatment effects were maintained over 124 weeks as demonstrated by reduction in LDL-C from week 12 in the parent study to week 112 in the open-label extension. A total of 2928 patients enrolled in OSLER-2. Repatha reduced LDL-C from baseline at week 12 compared with control. Treatment effects were maintained as demonstrated by reduction in LDL-C from week 12 to week 24 in the open-label extension. Repatha 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 1 and to week 24 in OSLER-2 compared with control. LDL-C and other lipid parameters returned to baseline within 12 weeks after discontinuation of Repatha at beginning of OSLER-1 without evidence of rebound.

TAUSSIG is an ongoing multicentre, open-label 5-year extension study to assess the long-term safety and efficacy of Repatha in patients with severe familial hypercholesterolaemia (FH), including homozygous familial hypercholesterolaemia (HoFH), who were treated with Repatha as an adjunct to other lipid-lowering therapies. A total of 102 severe FH patients and 96 HoFH patients enrolled in TAUSSIG. All patients in the study were initially treated with Repatha 420 mg once monthly except for those receiving apheresis at enrolment, who began with Repatha 420 mg 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. Repatha demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with severe FH (Table 4). Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of ongoing Repatha administration in patients with severe FH.

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**Table 4. Effect of Repatha on LDL-C in patients with severe FH – median percent change from baseline to OLE week 36**

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

OLE = open-label extension. N (n) = Number of evaluable patients (N) and patients with observed LDL values at specific schedule visit (n) in the Severe FH Interim Analysis Set.

**Homozygous familial hypercholesterolaemia**

TESLA was an international, multicentre, double-blind, randomised, placebo-controlled 12-week study of Repatha in 49 HoFH patients between 12 to 65 years of age (including 10 adolescent patients) evaluated for their response to 420 mg once monthly as an adjunct to other lipid-lowering therapies (e.g., statins, bile-acid sequestrants). Repatha 420 mg once monthly significantly reduced LDL-C and ApoB at week 12 compared with placebo (p<0.001) (Table 5). 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 HoFH.

**Table 5. Treatment effects of Repatha compared with placebo in patients with homozygous familial hypercholesterolaemia – mean percent change from baseline to week 12 (%; 95% CI)**

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

<sup>b</sup> p value <0.001 when compared with placebo.

**Efficacy in homozygous familial hypercholesterolaemia**

In TAUSSIG, Repatha demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with HoFH (overall, non-apheresis, apheresis) (

**Table 6).** Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of Repatha administration in patients with HoFH. Reductions in LDL-C and changes in other lipid parameters in 13 adolescent patients (12 to < 18 years of age) with HoFH were comparable to those in the overall HoFH study population.

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**Table 6. Effect of Repatha on LDL-C in patients with homozygous familial hypercholesterolaemia – mean percent change from baseline to OLE week 36**

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

OLE = open-label extension N (n) = Number of evaluable patients (N) and patients with observed LDL values at specific schedule visit (n) in the HoFH Interim Analysis Set (overall, non-apheresis, and apheresis).

**Other clinical information:**

- The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined.
- The type and incidence of adverse events observed in patients with LDL-C concentrations < 0.6 mmol/L and < 1.0 mmol/L were generally similar to those observed in patients with LDL-C concentrations ≥ 1.0 mmol/L. In an integrated analysis of phase 2 and 3 randomised placebo and active controlled studies of Repatha for up to 52 weeks duration, adverse events were reported in 51% (N=1609) of patients in the Repatha group who achieved an LDL < 0.6 mmol/L and 51% (N=2565) of patients in the Repatha group who achieved an LDL < 1.0 mmol/L compared with 52% (N=1339) of patients in the Repatha group with an LDL ≥ 1.0 mmol/L and 50% (N=2038) of patients in the control group with LDL ≥ 1.0 mmol/L.
- An integrated safety analysis of phase 2 and 3 randomised controlled studies of Repatha with statin therapy for up to 52 weeks duration was performed to assess alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and creatine kinase (CK) for patients with normal values at baseline. The incidence of ALT or AST > 5x upper limit of normal was 0.1% in both the Repatha (N=2523) and control (N=1249) groups. In the same studies, CK > 10 x upper limit of normal was 0.2% (N=2486) in the Repatha group and 0.1% (N=1217) in the control group.
- The safety of Repatha in the long-term, controlled studies was similar to the findings in the integrated analysis of phase 2 and 3 placebo and active controlled studies.

## INDICATIONS

Repatha is indicated as an adjunct to diet and exercise in:

### **Primary hypercholesterolaemia**

Repatha is indicated in adults with heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD):

- in combination with a statin or statin with other lipid lowering therapies, or
- in combination with other lipid-lowering therapies in patients who are statin-intolerant.

The effect of Repatha on cardiovascular morbidity and mortality has not been determined.

### **Homozygous familial hypercholesterolaemia**

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

## CONTRAINDICATIONS

Known hypersensitivity to evolocumab or any of the excipients found in Repatha.

## PRECAUTIONS

### **Allergic Reactions**

Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients treated with Repatha, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with Repatha, treat according to the standard of care, and monitor until signs and symptoms resolve.

### **Concomitant lipid-lowering therapies**

When using Repatha in combination with statins or other lipid-lowering therapies (e.g., ezetimibe), the prescriber should refer to the Contraindications and Precautions sections of the prescribing information for those medications.

### **Low LDL-C levels**

Although adverse consequences of very low LDL-C were not identified in the clinical trials, the long term effects of very low levels of LDL-C induced by Repatha are unknown.

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### **Immunogenicity**

In clinical studies, 0.1% of patients (7 out of 4846 patients with primary hypercholesterolaemia and 0 out of 80 patients with HoFH) treated with at least one dose of Repatha tested positive for binding antibody development (4 of these patients had transient antibodies). The patients whose sera tested positive for binding antibodies were further evaluated for 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.

### **Effects on fertility**

No data are available on the effect of Repatha on human fertility. In hamsters, there was no effect on male or female fertility (including oestrous cycling, sperm analysis, mating performance and embryonic development) when evolocumab was administered at dose levels up to 100 mg/kg every 2 weeks (AUC exposure estimate 7-fold higher than in patients receiving Repatha at 420 mg once every 2 weeks). In sexually mature cynomolgus monkeys, no effects were observed on reproductive organ histopathology, menstrual cycling, or sperm parameters following administration of evolocumab at dose levels up to 300 mg/kg weekly for 6 months (AUC exposure up to 133-fold higher than in patients receiving Repatha at 420 mg once every 2 weeks).

### **Use in pregnancy**

#### **Pregnancy Category: B1**

Category B1 refers to drugs where animal studies have not shown evidence of an increased occurrence of fetal damage and which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

In cynomolgus monkeys, no effects on embryo-fetal or postnatal development (up to 6 months of age) were observed when evolocumab was dosed throughout pregnancy at AUC exposure levels 5-fold higher than those achieved in patients receiving Repatha 420 mg once every 2 weeks.

Animal studies are not always predictive of human response. Therefore, it is not known whether Repatha can cause fetal harm when administered to a pregnant woman and Repatha should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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When Repatha is administered with a statin or other lipid-lowering therapies (e.g. ezetimibe) in women of childbearing potential, refer to the pregnancy section of the prescribing information for those medications.

### **Use in lactation**

It is not known whether Repatha is present in human milk. Many drugs are present in human milk and because of the potential for adverse effects in nursing infants from Repatha, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the potential benefit of the drug to the mother or the potential benefit of breast feeding to the infant.

### **Paediatric use**

The safety and effectiveness of Repatha have not been established in paediatric patients with primary hypercholesterolaemia and mixed dyslipidaemia. Fourteen adolescent patients aged 12 years and over have been included in HoFH clinical studies. No overall differences in safety or efficacy were observed between adolescent and adult patients with HoFH. Long term safety has not been established in children.

### **Use in the elderly**

Of the 6026 total number of patients in clinical studies of Repatha, 1779 (30%) were  $\geq 65$  years old, while 223 (4%) were  $\geq 75$  years old. No overall differences in safety or efficacy were observed between the elderly and younger patients.

### **Genotoxicity**

The mutagenic potential of Repatha has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

### **Carcinogenesis**

The carcinogenic potential of Repatha was evaluated in a lifetime study conducted in the hamster at dose levels up to 100 mg/kg every 2 weeks (AUC exposure 7-fold higher than in patients receiving Repatha at 420 mg once every 2 weeks). There were no evolocumab-related tumours. Expected serum LDL-C lowering was observed throughout the study.

### **Effects on laboratory tests**

None known

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**Hepatic impairment**

No dose adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh A or B). Repatha has not been studied in patients with severe hepatic impairment (Childs-Pugh C).

**Renal impairment**

No dose adjustment is necessary in patients with Chronic Kidney Disease (CKD) stages 2 and 3 (mild to moderate renal impairment) with eGFR < 90 to 30 mL/min/1.73m<sup>2</sup>. Repatha has not been studied in patients with CKD stages 4 and 5 (severe and very severe) with eGFR < 30 mL/min/1.73m<sup>2</sup>.

**INTERACTIONS WITH OTHER MEDICINES**

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

The pharmacokinetic interaction between statins and Repatha was evaluated in the Repatha clinical trials. An approximate 20% increase in the clearance of Repatha was observed in patients coadministered with statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9 which did not adversely impact the pharmacodynamic effect of Repatha on lipids. No statin dose adjustments are necessary when used in combination with Repatha.

**ADVERSE EFFECTS****Summary of the safety profile**

The safety of evolocumab was evaluated in 6026 patients with primary hypercholesterolaemia 4971 patients received evolocumab at any dose representing 4427 patient-years of exposure. In two clinical studies in 99 patients with homozygous familial hypercholesterolaemia, there were 63 patient-years of exposure to evolocumab 420 mg every two weeks or once monthly. 1824 patients were treated for 12 months or longer, 1801 patients with primary hypercholesterolaemia and 23 patients with homozygous familial hypercholesterolaemia. In clinical studies, the incidence of adverse events was similar between evolocumab and control groups. The adverse reactions associated with evolocumab were usually mild to moderate.

**Summary of Adverse Events**

Adverse events reported by preferred term for patients treated with evolocumab at an incidence rate ≥ 1.0% compared to any control, are shown in [Table 7](#).

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**Table 7. Adverse events occurring in patients treated with evolocumab compared to control\***

<b>Preferred Term Adverse Event</b>	<b>Any control (N = 2080) %</b>	<b>Any evolocumab (N = 3946) %</b>
Nasopharyngitis	4.8	5.9
Upper Respiratory Tract Infection	2.7	3.2
Headache	3.2	3.0
Back Pain	2.7	3.0
Myalgia	2.6	2.5
Arthralgia	2.2	2.3
Influenza	2.0	2.1
Nausea	1.8	2.1
Diarrhoea	2.4	2.0
Cough	1.3	2.0
Pain In Extremity	1.9	1.8
Fatigue	1.9	1.8
Muscle Spasms	1.8	1.7
Dizziness	1.6	1.6
Bronchitis	1.4	1.6
Urinary Tract Infection	1.6	1.5
Hypertension	1.3	1.4
Sinusitis	1.1	1.4
Musculoskeletal Pain	1.2	1.1
Oropharyngeal Pain	1.0	1.1
Blood Creatine Phosphokinase Increased	0.5	1.0
Gastroenteritis	0.8	1.0
Constipation	0.8	1.0
Injection Site Erythema	0.9	1.0
Injection Site Pain	0.5	1.0

\* Adverse events reported with evolocumab at an incident rate  $\geq$  1.0% compared to any control. Any control includes placebo and ezetimibe with or without placebo subjects

### *Neurocognitive events*

During the initial controlled parent studies neurocognitive events were reported for 0.1% patients on any evolocumab vs 0.3% patients on any control. During the open-label year 1 (control) period the incidence was 0.6% evolocumab plus standard of care vs 0.2% standard of care alone. Most of the neurocognitive events were mild or moderate in severity.

### *Musculoskeletal events*

Musculoskeletal adverse events were reported in 14.7% of patients in the any evolocumab group and 13.7% of patients in the any control group. The most common

adverse events that occurred at a rate greater than any control were back pain and arthralgia.

### **Summary of Adverse Reactions**

Adverse reactions reported in  $\geq 2\%$  of patients treated with evolocumab and at an incidence greater than any control in studies of evolocumab, are shown in [Table 8](#).

**Table 8. Adverse reactions occurring in patients treated with evolocumab compared to placebo and control\***

<b>Body System/Organ Class</b> Adverse Reaction	Placebo (N = 1526) %	Any control (N = 2080) %	Any evolocumab (N = 3946) %
<b>INFECTIONS AND INFESTATIONS</b>			
Nasopharyngitis	5.0	4.8	5.9
Upper Respiratory Tract Infection	2.8	2.7	3.2
Influenza	2.1	2.0	2.1
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
Back Pain	2.9	2.7	3.0
Arthralgia	2.2	2.2	2.3
<b>GASTROINTESTINAL DISORDERS</b>			
Nausea	1.6	1.8	2.1

\* Adverse reactions reported in at least 2% of patients receiving evolocumab and more frequently in the evolocumab group than any control

#### *Injection site reactions*

Injection site reactions have been reported in patients treated with evolocumab (3.0% control vs 3.3% evolocumab). The most common injection site reactions were erythema, pain and bruising. Most of these reactions were mild in severity.

### **Line listing of Adverse Reactions**

A line listing of adverse reactions reported in  $<1\%$  of patients treated with evolocumab to a 0.4% cut off, at an incidence greater than any control, are shown below:

**Blood and lymphatic system disorders:** Anaemia ( $<0.1\%$  control vs 0.4% evolocumab).

**Cardiac disorders:** Palpitations (0.3% control vs 0.6% evolocumab).

**Gastrointestinal disorders:** Vomiting (0.7% control vs 0.9% evolocumab), Abdominal pain upper, (0.7% control vs 0.8% evolocumab), Dyspepsia (0.4% control vs 0.6% evolocumab), Abdominal distension (0.4% control vs 0.6% evolocumab) and Flatulence (0.3% control vs 0.5% evolocumab).

**General disorders and administrative site conditions:** Chest pain (0.4% control vs 0.5% evolocumab), Pyrexia (0.3% control vs 0.4% evolocumab), Asthenia (0.2% control vs 0.4% evolocumab), Injection site induration (< 0.1% control vs 0.4% evolocumab) and Non cardiac-chest pain (0.3% control vs 0.4% evolocumab).

**Infections and infestations:** Pneumonia (0.2% control vs 0.5% evolocumab), Viral upper respiratory tract infection (0.3% control vs 0.4% evolocumab), Gastroenteritis viral (0.3% control vs 0.4% evolocumab) and Tooth infection (0.2% control vs 0.4% evolocumab).

**Injury, poisoning and procedural complications:** Arthropod bite (0.1% control vs 0.5% evolocumab) and Laceration (0.3% control vs 0.4% evolocumab).

**Metabolism and nutrition disorders:** Gout (0.1% control vs 0.4% evolocumab) and Decreased appetite (0.1% control vs 0.4% evolocumab).

**Musculoskeletal and connective tissue disorders:** Osteoarthritis (0.4% control vs 0.6% evolocumab), Neck pain (0.2% control vs 0.5% evolocumab), Tendonitis (0.2% control vs 0.5% evolocumab) and Musculoskeletal chest pain (0.3% control vs 0.4% evolocumab).

**Nervous system disorders:** Paraesthesia (0.4% control vs 0.6% evolocumab) and Syncope (0.3% control vs 0.4% evolocumab).

**Psychiatric disorders:** Insomnia (0.5% control vs 0.7% evolocumab) and Anxiety (0.2% control vs 0.5% evolocumab).

**Respiratory, thoracic and mediastinal disorders:** Epistaxis (0.2% control vs 0.4% evolocumab), Sinus congestion (0.3% control vs 0.4% evolocumab).

**Skin and subcutaneous tissue disorders:** Rash (0.7% control vs. 0.9% evolocumab), Eczema (0.1% control vs 0.4% evolocumab), Urticaria (0.1% control vs. 0.4% evolocumab).

The safety profile in the HoFH population was consistent with that demonstrated in the primary hypercholesterolaemia population.

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**Post marketing experience**

Not applicable at this time.

**DOSAGE AND ADMINISTRATION****Dosage****Primary Hypercholesterolaemia (HeFH or clinical atherosclerotic CVD) :**

The recommended dose for Repatha is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.

**Homozygous familial hypercholesterolaemia:**

The initial recommended dose for Repatha is 420 mg once monthly. The dose can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

**Patients with renal impairment**

No dose adjustment is necessary in patients with mild to moderate (stages 2 and 3) renal impairment. Repatha has not been studied in patients with more severe (stages 4 or 5) renal impairment (eGFR < 30 mL/min/1.73m<sup>2</sup>).

**Patients with hepatic impairment**

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Repatha has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

**Elderly patients**

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

**Administration**

Administration should be performed by an individual who has been trained to administer the product.

Prior to subcutaneous administration, allow Repatha to sit at room temperature for at least 30 minutes for the pre-filled pen or 45 minutes for the automated mini-doser (AMD). Do not warm in any other way.

Avoid vigorous shaking the product.

Visually inspect the solution for particles and discolouration. Do not use if the solution is discoloured, cloudy, or if flakes or particles are present.

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Doses may be administered in the upper arm, thigh, or abdomen. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard.

Repatha is for single use in one patient only. Discard any residue.

Comprehensive instructions for the administration of Repatha are provided in the Instructions for Use.

Indication	Recommended Dosage and Frequency	Method of Administration
Primary Hypercholesterolaemia (Heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD))	140 mg every 2 weeks	One single-use pre-filled pen (SureClick®)
	420 mg once monthly	One single-use automated mini-doser (AMD) with 3.5 mL prefilled cartridge or Three single-use pre-filled pens (SureClick®) administered consecutively within 30 minutes
Homozygous Familial Hypercholesterolaemia	Initial dose is 420 mg once monthly. The dose can be increased to 420 mg every 2 weeks if a clinical meaningful response is not achieved in 12 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with apheresis schedule.	One single-use automated mini-doser (AMD) with 3.5 mL prefilled cartridge or Three single-use pre-filled pens (SureClick®) administered consecutively within 30 minutes

## OVERDOSAGE

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.

For information on the management of overdose, contact the Poison Information Centre on 131126.

## PRESENTATION AND STORAGE CONDITIONS

### Presentation

The needle cover of the glass pre-filled syringe\* and the pre-filled pen is made from dry natural rubber (a derivative of latex).

Repatha is provided as a:

- 1 mL solution (140 mg/mL evolocumab) in a single use pre-filled syringe made from type I glass with stainless steel needle, supplied as a 1-pack.\*  
\* Not available in Australia
- 1 mL solution (140 mg/mL evolocumab) in a single use pre-filled pen with type 1 glass syringe and stainless steel needle; supplied as a 1-pack, 2-pack, and 3-pack.
- 3.5 mL solution (120 mg/mL) in a single-use prefilled cartridge assembly made from Crystal Zenith® resin which is co-packaged with an administration device (AMD). The administration device is a compact, sterile, single-use, disposable, injection device intended for use only with the provided 3.5 mL pre-filled cartridge assembly; supplied as a 1-pack.

### Storage

**Store refrigerated at 2°C to 8°C in the original carton.**

If removed from the refrigerator, Repatha should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days.

Protect Repatha from direct light and do not expose to temperatures above 25°C.

Do not freeze.

Do not shake.

### **NAME AND ADDRESS OF THE SPONSOR**

Amgen Australia Pty Ltd

Level 7, 123 Epping Road

North Ryde, NSW 2113

ABN 31 051 057 428

Medical Information: 1800 803 638.

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**POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (S4)

**DATE OF FIRST INCLUSION IN THE ARTG:**

9 December 2015

**DATE OF MOST RECENT AMENDMENT:**

28 March 2017

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