

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REPATHA® safely and effectively. See full prescribing information for REPATHA.

REPATHA (evolocumab) injection, for subcutaneous use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2)	12/2017
Contraindications (4)	10/2018
Warnings and Precautions (5.1)	10/2018

INDICATIONS AND USAGE

REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated:

- to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease. (1.1)
- as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C). (1.2)
- as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. (1.3)

DOSAGE AND ADMINISTRATION

- Administer subcutaneously. (2.1)
- Adults with established cardiovascular disease or primary hyperlipidemia (including heterozygous familial hypercholesterolemia): 140 mg every 2 weeks or 420 mg once monthly in abdomen, thigh, or upper arm. (2.1)
- HoFH: 420 mg once monthly. (2.1)
- The 420 mg dose of REPATHA can be administered:
 - over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or
 - by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled syringe. (2.2)
- See Dosage and Administration for important administration instructions. (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 140 mg/mL solution in a single-use prefilled syringe (3)
- Injection: 140 mg/mL solution in a single-use prefilled SureClick® autoinjector (3)
- Injection: 420 mg/3.5 mL solution in a single-use Pushtronex® system (on-body infusor with prefilled cartridge) (3)

CONTRAINDICATIONS

Patients with a history of a serious hypersensitivity reaction to REPATHA. (4)

WARNINGS AND PRECAUTIONS

Allergic Reactions: Angioedema, rash, and urticaria have occurred. 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. (5.1)

ADVERSE REACTIONS

Common adverse reactions in clinical trials in primary hyperlipidemia (including heterozygous familial hypercholesterolemia) (> 5% of patients treated with REPATHA and occurring more frequently than placebo): nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. (6)

Common adverse reactions in the cardiovascular outcomes trial (> 5% of patients treated with REPATHA and occurring more frequently than placebo): diabetes mellitus, nasopharyngitis and upper respiratory tract infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Prevention of Cardiovascular Events

In adults with established cardiovascular disease, REPATHA[®] is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization.

1.2 Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)

REPATHA is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).

1.3 Homozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended subcutaneous dosage of REPATHA in adults with established cardiovascular disease or in adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) is either 140 mg every 2 weeks OR 420 mg once monthly, based on patient preference for dosing frequency and injection volume. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

The recommended subcutaneous dosage of REPATHA in patients with HoFH is 420 mg once monthly. In patients with HoFH, measure LDL-C levels 4 to 8 weeks after starting REPATHA, since response to therapy will depend on the degree of LDL-receptor function.

When monitoring LDL-C for patients receiving REPATHA 420 mg once monthly, note that LDL-C can vary considerably during the dosing interval in some patients [*see Clinical Studies (14)*].

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

- If an every-2-week dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.
- If a once-monthly dose is not administered within 7 days, instruct the patient to administer the dose and start a new schedule based on this date.

2.2 Important Administration Instructions

- The 420 mg dose of REPATHA can be administered:
 - over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or

- by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled syringe.
- Provide proper training to patients and/or caregivers on how to prepare and administer REPATHA prior to use, according to the Instructions for Use, including aseptic technique. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use REPATHA.
- Keep REPATHA in the refrigerator. Prior to use, allow REPATHA to warm to room temperature for at least 30 minutes for the single-use prefilled autoinjector or single-use prefilled syringe and for at least 45 minutes for the single-use on-body infusor with prefilled cartridge. Do not warm in any other way. Alternatively, for patients and caregivers, REPATHA can be kept at room temperature at 68°F to 77°F (20°C to 25°C) in the original carton. However, under these conditions, REPATHA must be used within 30 days [*see How Supplied/Storage and Handling (16)*].
- Visually inspect REPATHA for particles and discoloration prior to administration. REPATHA is a clear to opalescent, colorless to pale yellow solution. Do not use if the solution is cloudy or discolored or contains particles.
- Administer REPATHA subcutaneously into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated using a single-use prefilled syringe, single-use prefilled autoinjector, or single-use on-body infusor with prefilled cartridge.
- Do not co-administer REPATHA with other injectable drugs at the same administration site.
- Rotate the site of each subcutaneous administration.

3 DOSAGE FORMS AND STRENGTHS

REPATHA is a sterile, clear to opalescent, colorless to pale yellow solution available as follows:

- Injection: 140 mg/mL solution in a single-use prefilled syringe
- Injection: 140 mg/mL solution in a single-use prefilled SureClick® autoinjector
- Injection: 420 mg/3.5 mL solution in a single-use Pushtronex® system (on-body infusor with prefilled cartridge)

4 CONTRAINDICATIONS

REPATHA is contraindicated in patients with a history of a serious hypersensitivity reaction to REPATHA. Serious hypersensitivity reactions including angioedema have occurred in patients treated with REPATHA [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

Hypersensitivity reactions (e.g., angioedema, 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 [*see Contraindications (4)*].

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the label:

- Allergic Reactions [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Adults with Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The data described below reflect exposure to REPATHA in 8 placebo-controlled trials that included 2651 patients treated with REPATHA, including 557 exposed for 6 months and 515 exposed for 1 year (median treatment duration of 12 weeks). The mean age of the population was 57 years, 49% of the population were women, 85% White, 6% Black, 8% Asians, and 2% other races.

Adverse Reactions in a 52-Week Controlled Trial

In a 52-week, double-blind, randomized, placebo-controlled trial (Study 3 [DESCARTES, NCT01516879]), 599 patients received 420 mg of REPATHA subcutaneously once monthly [see Clinical Studies (14.2)]. The mean age was 56 years (range: 22 to 75 years), 23% were older than 65 years, 52% women, 80% White, 8% Black, 6% Asian; 6% identified as Hispanic ethnicity. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients in DESCARTES, are shown in Table 1. Adverse reactions led to discontinuation of treatment in 2.2% of REPATHA-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to REPATHA treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for REPATHA and placebo, respectively).

Table 1. Adverse Reactions Occurring in Greater than or Equal to 3% of REPATHA-treated Patients and More Frequently than with Placebo in DESCARTES

	Placebo (N = 302) %	REPATHA (N = 599) %
Nasopharyngitis	9.6	10.5
Upper respiratory tract infection	6.3	9.3
Influenza	6.3	7.5
Back pain	5.6	6.2
Injection site reactions [†]	5.0	5.7
Cough	3.6	4.5
Urinary tract infection	3.6	4.5
Sinusitis	3.0	4.2
Headache	3.6	4.0
Myalgia	3.0	4.0
Dizziness	2.6	3.7
Musculoskeletal pain	3.0	3.3
Hypertension	2.3	3.2

	Placebo (N = 302) %	REPATHA (N = 599) %
Diarrhea	2.6	3.0
Gastroenteritis	2.0	3.0

†includes erythema, pain, bruising

Adverse Reactions in Seven Pooled 12-Week Controlled Trials

In seven pooled 12-week, double-blind, randomized, placebo-controlled trials, 993 patients received 140 mg of REPATHA subcutaneously every 2 weeks and 1059 patients received 420 mg of REPATHA subcutaneously monthly. The mean age was 57 years (range: 18 to 80 years), 29% were older than 65 years, 49% women, 85% White, 5% Black, 9% Asian; 5% identified as Hispanic ethnicity. Adverse reactions reported in at least 1% of REPATHA-treated patients, and more frequently than in placebo-treated patients, are shown in Table 2.

Table 2. Adverse Reactions Occurring in Greater than 1% of REPATHA-treated Patients and More Frequently than with Placebo in Pooled 12-Week Trials

	Placebo (N = 1224) %	REPATHA[†] (N = 2052) %
Nasopharyngitis	3.9	4.0
Back pain	2.2	2.3
Upper respiratory tract infection	2.0	2.1
Arthralgia	1.6	1.8
Nausea	1.2	1.8
Fatigue	1.0	1.6
Muscle spasms	1.2	1.3
Urinary tract infection	1.2	1.3
Cough	0.7	1.2
Influenza	1.1	1.2
Contusion	0.5	1.0

†140 mg every 2 weeks and 420 mg once monthly combined

Adverse Reactions in Eight Pooled Controlled Trials (Seven 12-Week Trials and One 52-Week Trial)

The adverse reactions described below are from a pool of the 52-week trial (DESCARTES) and seven 12-week trials. The mean and median exposure durations of REPATHA in this pool of eight trials were 20 weeks and 12 weeks, respectively.

Local Injection Site Reactions

Injection site reactions occurred in 3.2% and 3.0% of REPATHA-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection site reactions in REPATHA-treated patients and placebo-treated patients were 0.1% and 0%, respectively.

Allergic Reactions

Allergic reactions occurred in 5.1% and 4.7% of REPATHA-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for REPATHA and

placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).

Adverse Reactions in the Cardiovascular Outcomes Trial

In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial (Study 1 [REPATHA Cardiovascular Outcomes Trial, FOURIER, NCT01764633]), 27,525 patients received at least one dose of REPATHA or placebo [see *Clinical Studies (14.1)*]. The mean age was 62.5 years (range: 40 to 86 years), 45% were 65 years or older, 9% were 75 years or older, 25% women, 85% White, 2% Black and 10% Asian; 8% identified as Hispanic ethnicity. Patients were exposed to REPATHA or placebo for a median of 24.8 months; 91% of patients were exposed for ≥ 12 months, 54% were exposed for ≥ 24 months and 5% were exposed for ≥ 36 months.

The safety profile of REPATHA in this trial was generally consistent with the safety profile described above in the 12- and 52-week controlled trials involving patients with primary hyperlipidemia (including HeFH). Serious adverse events occurred in 24.8% and 24.7% of REPATHA-treated and placebo-treated patients, respectively. Adverse events led to discontinuation of study treatment in 4.4% of patients assigned to REPATHA and 4.2% assigned to placebo. Common adverse reactions ($> 5\%$ of patients treated with REPATHA and occurring more frequently than placebo) included diabetes mellitus (8.8% REPATHA, 8.2% placebo), nasopharyngitis (7.8% REPATHA, 7.4% placebo), and upper respiratory tract infection (5.1% REPATHA, 4.8% placebo).

Among the 16,676 patients without diabetes mellitus at baseline, the incidence of new-onset diabetes mellitus during the trial was 8.1% in patients assigned to REPATHA compared with 7.7% in those assigned to placebo.

Adverse Reactions in Patients with Homozygous Familial Hypercholesterolemia

In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (Study 6 [TESLA, NCT01588496]), 33 patients received 420 mg of REPATHA subcutaneously once monthly [see *Clinical Studies (14.3)*]. The mean age was 31 years (range: 13 to 57 years), 49% were women, 90% White, 4% Asian, and 6% other. The adverse reactions that occurred in at least two (6.1%) REPATHA-treated patients, and more frequently than in placebo-treated patients, included:

- Upper respiratory tract infection (9.1% versus 6.3%)
- Influenza (9.1% versus 0%)
- Gastroenteritis (6.1% versus 0%)
- Nasopharyngitis (6.1% versus 0%)

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to REPATHA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of REPATHA has been evaluated using an electrochemiluminescent bridging screening immunoassay for the detection of binding anti-drug antibodies. For patients whose sera tested

positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In a pool of placebo- and active-controlled clinical trials, 0.3% (48 out of 17,992) of patients treated with at least one dose of REPATHA tested positive for the development of binding antibodies. Patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies; none of the patients tested positive for neutralizing antibodies.

There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of REPATHA, but the long-term consequences of continuing REPATHA treatment in the presence of anti-drug binding antibodies are unknown.

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use of REPATHA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Allergic reactions: Angioedema

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REPATHA during pregnancy.

Please contact 1-877-311-8972 or <https://mothertobaby.org/ongoing-study/repatha/> to enroll in or to obtain information about the registry.

Risk Summary

There are no data available on use of REPATHA in pregnant women to inform a drug-associated risk. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered evolocumab from organogenesis through parturition at dose exposures up to 12 times the exposure at the maximum recommended human dose of 420 mg every month. In a similar study with another drug in the PCSK9 inhibitor antibody class, humoral immune suppression was observed in infant monkeys exposed to that drug in utero at all doses. The exposures where immune suppression occurred in infant monkeys were greater than those expected clinically. No assessment for immune suppression was conducted with evolocumab in infant monkeys. Measurable evolocumab serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that evolocumab, like other IgG antibodies, crosses the placental barrier. FDA's experience with monoclonal antibodies in humans indicates that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester. Consider the benefits and risks of REPATHA and possible risks to the fetus before prescribing REPATHA to pregnant women.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In cynomolgus monkeys, no effects on embryo-fetal or postnatal development (up to 6 months of age) were observed when evolocumab was dosed during organogenesis to parturition at 50 mg/kg once every 2 weeks by the subcutaneous route at exposures 30- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. No test of humoral immunity in infant monkeys was conducted with evolocumab.

8.2 Lactation

Risk Summary

There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REPATHA and any potential adverse effects on the breastfed infant from REPATHA or from the underlying maternal condition. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

8.4 Pediatric Use

The safety and effectiveness of REPATHA in combination with diet and other LDL-C-lowering therapies in adolescents with HoFH who require additional lowering of LDL-C were established based on data from a 12-week, placebo-controlled trial that included 10 adolescents (ages 13 to 17 years old) with HoFH [see *Clinical Studies (14.3)*]. In this trial, 7 adolescents received REPATHA 420 mg subcutaneously once monthly and 3 adolescents received placebo. The effect of REPATHA on LDL-C was generally similar to that observed among adult patients with HoFH. Including experience from open-label, uncontrolled studies, a total of 14 adolescents with HoFH have been treated with REPATHA, with a median exposure duration of 9 months. The safety profile of REPATHA in these adolescents was similar to that described for adult patients with HoFH.

The safety and effectiveness of REPATHA have not been established in pediatric patients with HoFH who are younger than 13 years old.

The safety and effectiveness of REPATHA have not been established in pediatric patients with primary hyperlipidemia or HeFH.

8.5 Geriatric Use

In controlled trials, 7656 (41%) patients treated with REPATHA were ≥ 65 years old and 1500 (8%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is needed in patients with renal impairment. [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment (Child-Pugh A or B). No data are available in patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

11 DESCRIPTION

Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) directed against human proprotein convertase subtilisin kexin 9 (PCSK9). Evolocumab has an approximate molecular weight (MW) of 144 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

REPATHA is a sterile, preservative-free, clear to opalescent, colorless to pale yellow solution for subcutaneous administration. Each 1 mL single-use prefilled syringe and single-use prefilled SureClick® autoinjector contains 140 mg evolocumab, acetate (1.2 mg), polysorbate 80 (0.1 mg), proline (25 mg) in Water for Injection, USP. Sodium hydroxide may be used to adjust to a pH of 5.0. Each single-use Pushtronex® system (on-body infusor with prefilled cartridge) delivers a 3.5 mL solution containing 420 mg evolocumab, acetate (4.2 mg), polysorbate 80 (0.35 mg), proline (89 mg) in Water for Injection, USP. Sodium hydroxide may be used to adjust to a pH of 5.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Evolocumab is a human monoclonal IgG2 directed against human proprotein convertase subtilisin kexin 9 (PCSK9). Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, evolocumab increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels.

12.2 Pharmacodynamics

Following single subcutaneous administration of 140 mg or 420 mg of evolocumab, maximum suppression of circulating unbound PCSK9 occurred by 4 hours. Unbound PCSK9 concentrations returned toward baseline when evolocumab concentrations decreased below the limit of quantitation.

12.3 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) 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 evolocumab 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 intravenous dose, the mean (SD) steady-state volume of distribution was estimated to be 3.3 (0.5) L.

Metabolism and Elimination

Two elimination phases were observed for REPATHA. At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination of REPATHA is largely through a non-saturable proteolytic pathway. REPATHA was estimated to have an effective half-life of 11 to 17 days.

Specific Populations

The pharmacokinetics of evolocumab were not affected by age, gender, race, or creatinine clearance across all approved populations [*see Use in Specific Populations (8.5)*].

The exposure of evolocumab decreased with increasing body weight. These differences are not clinically meaningful.

Renal Impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of evolocumab.

In a clinical trial of 18 patients with either normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m², n = 6), severe renal impairment (eGFR < 30 mL/min/1.73 m², n = 6), or end-stage renal disease (ESRD) receiving hemodialysis (n = 6), exposure to evolocumab after a single 140 mg subcutaneous dose was decreased in patients with severe renal impairment or ESRD receiving hemodialysis. Reductions in PCSK9 levels in patients with severe renal impairment or ESRD receiving hemodialysis was similar to those with normal renal function [*see Use in Specific Populations (8.6)*].

Hepatic Impairment

Following a single 140 mg subcutaneous dose of evolocumab in patients with mild or moderate hepatic impairment, a 20-30% lower mean C_{max} and 40-50% lower mean AUC were observed as compared to healthy patients; however, no dose adjustment is necessary in these patients.

Pregnancy

The effect of pregnancy on evolocumab pharmacokinetics has not been studied [*see Use in Specific Populations (8.1)*].

Drug Interaction Studies

An approximately 20% decrease in the C_{max} and AUC of evolocumab was observed in patients co-administered with a high-intensity statin regimen. This difference is not clinically meaningful and does not impact dosing recommendations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of evolocumab was evaluated in a lifetime study conducted in the hamster at dose levels of 10, 30, and 100 mg/kg administered every 2 weeks. There were no evolocumab-related tumors at the highest dose at systemic exposures up to 38- and 15-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. The mutagenic potential of evolocumab has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

There were no adverse effects on fertility (including estrous cycling, sperm analysis, mating performance, and embryonic development) at the highest dose in a fertility and early embryonic developmental toxicology study in hamsters when evolocumab was subcutaneously administered at 10, 30, and 100 mg/kg every 2 weeks. The highest dose tested corresponds to systemic exposures up to 30- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. In addition, there were no adverse evolocumab-related effects on surrogate markers of fertility (reproductive organ histopathology, menstrual cycling, or sperm parameters) in a 6-month chronic toxicology study in sexually mature monkeys subcutaneously administered evolocumab at 3, 30, and 300 mg/kg once weekly. The highest dose tested corresponds to 744- and 300-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC.

13.2 Animal Toxicology and/or Pharmacology

During a 3-month toxicology study of 10 and 100 mg/kg once every 2 weeks evolocumab in combination with 5 mg/kg once daily rosuvastatin in adult monkeys, there were no effects of evolocumab on the humoral immune response to keyhole limpet hemocyanin (KLH) after 1 to 2 months exposure. The highest dose tested corresponds to exposures 54- and 21-fold higher than the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. Similarly, there were no effects of evolocumab on the humoral immune response to KLH (after 3 to 4 months exposure) in a 6-month study in cynomolgus monkeys at dose levels up to 300 mg/kg once weekly evolocumab corresponding to exposures 744- and 300-fold greater than the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC.

14 CLINICAL STUDIES

14.1 Prevention of Cardiovascular Events

Study 1 (FOURIER, NCT01764633) was a double-blind, randomized, placebo-controlled, event-driven trial in 27,564 (13,784 REPATHA, 13,780 placebo) adult patients with established cardiovascular disease and with LDL-C \geq 70 mg/dL and/or non-HDL-C \geq 100 mg/dL despite high- or moderate-intensity statin therapy. Patients were randomly assigned 1:1 to receive either subcutaneous injections of REPATHA (140 mg every 2 weeks or 420 mg once monthly) or placebo; 86% used the every-2-week regimen throughout the trial. The median follow-up duration was 26 months. Overall, 99.2% of patients were followed until the end of the trial or death.

The mean (SD) age at baseline was 63 (9) years, with 45% being at least 65 years old; 25% were women. The trial population was 85% White, 2% Black, and 10% Asian; 8% identified as Hispanic ethnicity. Regarding prior diagnoses of cardiovascular disease, 81% had prior myocardial infarction, 19% prior non-hemorrhagic stroke, and 13% had symptomatic peripheral arterial disease. Selected additional baseline risk factors included hypertension (80%), diabetes mellitus (1% type 1; 36% type 2), current daily cigarette smoking (28%), New York Heart Association class I or II congestive heart failure (23%), and eGFR $<$ 60 mL/min per 1.73 m² (6%). Most patients were on a high- (69%) or moderate-intensity (30%) statin therapy at baseline, and 5% were also taking ezetimibe. Most patients were taking at least one other cardiovascular medication including anti-platelet agents (93%), beta blockers (76%), angiotensin converting enzyme (ACE) inhibitors (56%), or angiotensin receptor blockers (23%). On stable background lipid-lowering therapy, the median [Q1, Q3] LDL-C at baseline was 92 [80, 109] mg/dL; the mean (SD) was 98 (28) mg/dL.

REPATHA significantly reduced the risk for the primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary

revascularization; $p < 0.0001$) and the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, or stroke; $p < 0.0001$). The Kaplan-Meier estimates of the cumulative incidence of the primary and key secondary composite endpoints over time are shown in Figure 1 and Figure 2 below.

The results of primary and secondary efficacy endpoints are shown in Table 3 below.

Table 3. Effect of REPATHA on Cardiovascular Events in Patients with Established Cardiovascular Disease in FOURIER

	Placebo		REPATHA		REPATHA vs. Placebo
	N = 13780 n (%)	Incidence Rate (per 100 patient years)	N = 13784 n (%)	Incidence Rate (per 100 patient years)	Hazard Ratio (95% CI)
Primary composite endpoint					
Time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina	1563 (11.3)	5.2	1344 (9.8)	4.5	0.85 (0.79, 0.92)
Key secondary composite endpoint					
Time to first occurrence of cardiovascular death, myocardial infarction, stroke	1013 (7.4)	3.4	816 (5.9)	2.7	0.80 (0.73, 0.88)
Other secondary endpoints					
Time to cardiovascular death	240 (1.7)	0.8	251 (1.8)	0.8	1.05 (0.88, 1.25)
Time to death by any cause ^a	426 (3.1)	1.4	444 (3.2)	1.5	1.04 (0.91, 1.19)
Time to first fatal or non-fatal myocardial infarction	639 (4.6)	2.1	468 (3.4)	1.6	0.73 (0.65, 0.82)
Time to first fatal or non-fatal stroke	262 (1.9)	0.9	207 (1.5)	0.7	0.79 (0.66, 0.95)
Time to first coronary revascularization	965 (7.0)	3.2	759 (5.5)	2.5	0.78 (0.71, 0.86)
Time to first hospitalization for unstable angina ^b	239 (1.7)	0.8	236 (1.7)	0.8	0.99 (0.82, 1.18)
^a Time to death by any cause is not a component of either the primary composite endpoint or key secondary composite endpoint.					
^b Not a prespecified endpoint; an ad hoc analysis was performed to ensure results are provided for each individual component of the primary endpoint.					

Figure 1. Estimated Cumulative Incidence of Primary Composite Endpoint Over 3 Years in FOURIER

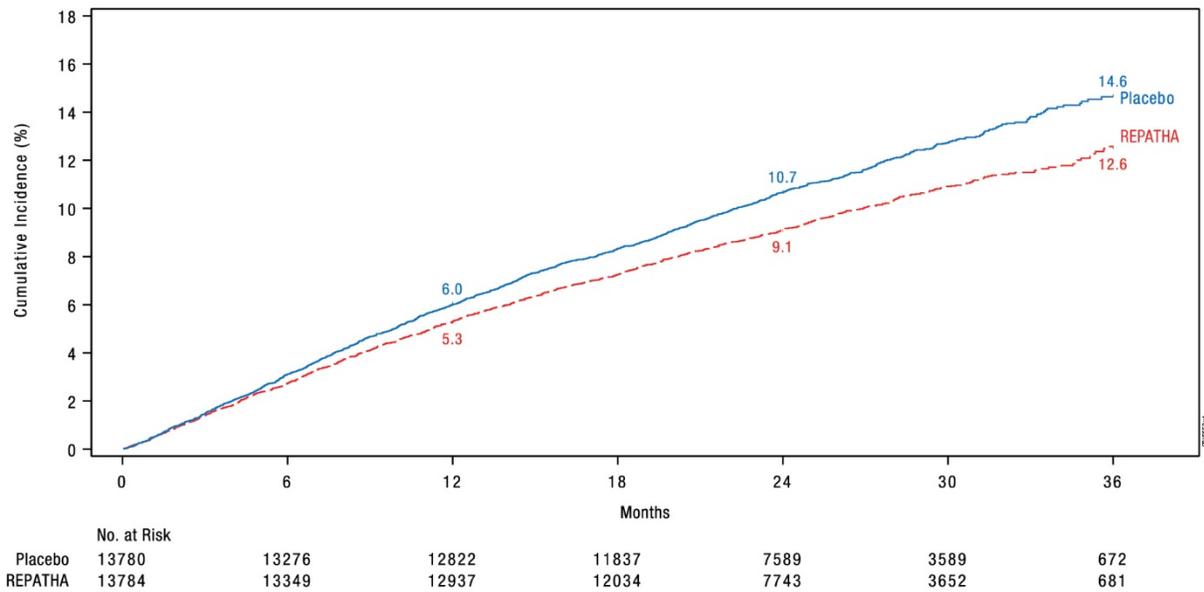
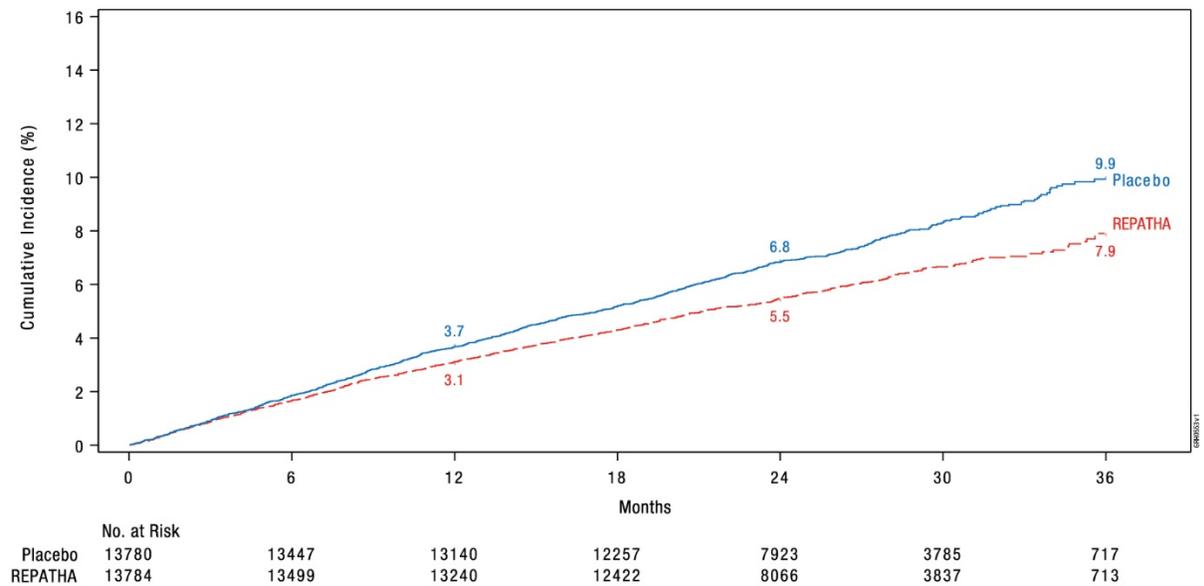


Figure 2. Estimated Cumulative Incidence of Key Secondary Composite Endpoint Over 3 Years in FOURIER



The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -63% (95% CI: -63%, -62%) and from baseline to Week 72 was -57% (95% CI: -58%, -56%). At Week 48, the median [Q1, Q3] LDL-C was 26 [15, 46] mg/dL in the REPATHA group, with 47% of patients having LDL-C < 25 mg/dL.

Considering all assessments, among the patients treated with REPATHA, 10401 (76%) had at least one LDL-C value < 25 mg/dL. Although not a randomized comparison, the safety profile was similar between

REPATHA-treated patients with post-baseline LDL-C < 25 mg/dL compared with REPATHA-treated patients with higher post-baseline LDL-C (LDL-C ≥ 40 mg/dL).

In EBBINGHAUS (NCT02207634), a substudy of 1974 patients enrolled in the FOURIER trial, REPATHA was non-inferior to placebo on selected cognitive function domains as assessed with the use of neuropsychological function tests over a median follow-up of 19 months.

14.2 Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)

Study 2 (LAPLACE-2, NCT01763866) was a multicenter, double-blind, randomized controlled 12-week trial in which patients were initially randomized to an open-label specific statin regimen for a 4-week lipid stabilization period followed by random assignment to subcutaneous injections of REPATHA 140 mg every 2 weeks, REPATHA 420 mg once monthly, or placebo for 12 weeks. The trial included 1896 patients with hyperlipidemia who received REPATHA, placebo, or ezetimibe as add-on therapy to daily doses of statins (atorvastatin, rosuvastatin, or simvastatin). Ezetimibe was also included as an active control only among those assigned to background atorvastatin. Overall, the mean age at baseline was 60 years (range: 20 to 80 years), 35% were ≥ 65 years old, 46% women, 94% White, 4% were Black, and 1% Asian; 5% identified as Hispanic or Latino ethnicity. After 4 weeks of background statin therapy, the mean baseline LDL-C ranged between 77 and 127 mg/dL across the five background therapy arms.

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -71% (95% CI: -74%, -67%; $p < 0.0001$) and -63% (95% CI: -68%, -57%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. The difference between REPATHA and ezetimibe in mean percent change in LDL-C from baseline to Week 12 was -45% (95% CI: -52%, -39%; $p < 0.0001$) and -41% (95% CI: -47%, -35%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 4 and Figure 3.

Table 4. Effect of REPATHA on Lipid Parameters in Patients with Hyperlipidemia on Background Statin Regimens (Mean % Change from Baseline to Week 12 in LAPLACE-2)

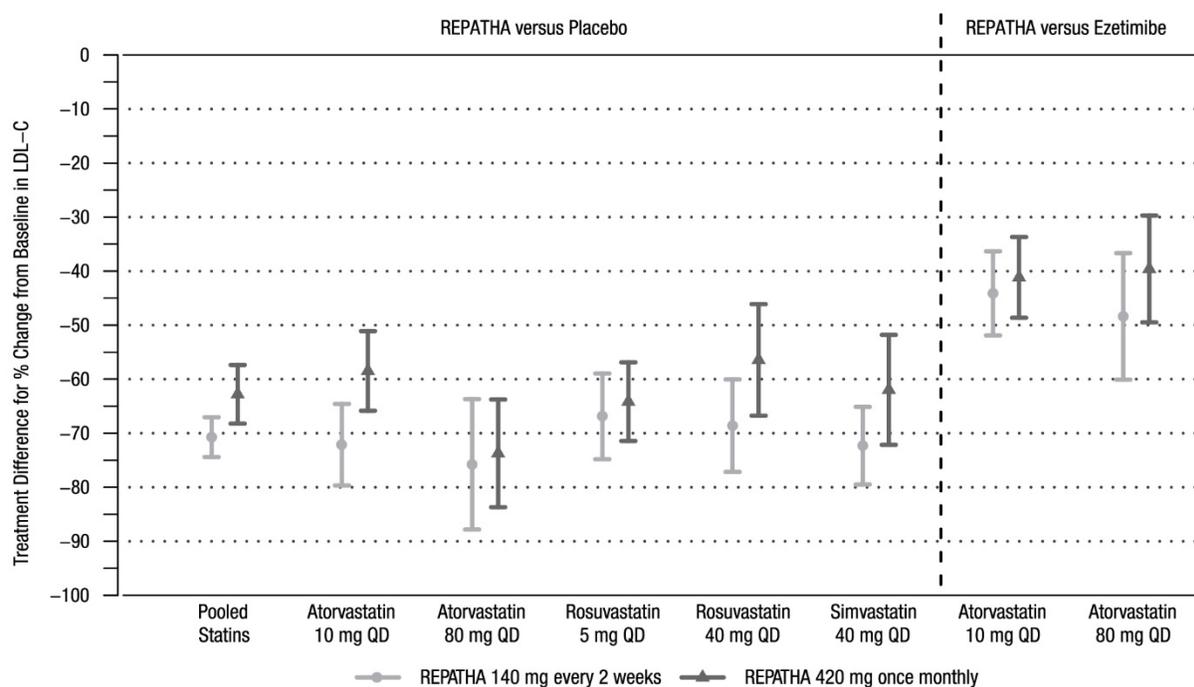
Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
REPATHA every 2 weeks vs. Placebo every 2 weeks (Background statin: atorvastatin 10 mg or 80 mg; rosuvastatin 5 mg or 40 mg; simvastatin 40 mg)				
Placebo every 2 weeks (n = 281)	8	6	5	4
REPATHA 140 mg every 2 weeks [†] (n = 555)	-63	-53	-49	-36
Mean difference from placebo (95% CI)	-71 (-74, -67)	-59 (-62, -55)	-55 (-58, -52)	-40 (-43, -38)
REPATHA once monthly vs. Placebo once monthly (Background statin: atorvastatin 10 mg or 80 mg; rosuvastatin 5 mg or 40 mg; simvastatin 40 mg)				
Placebo once monthly (n = 277)	4	5	3	2
REPATHA 420 mg once monthly (n = 562)	-59	-50	-46	-34
Mean difference from placebo (95% CI)	-63 (-68, -57)	-54 (-58, -50)	-50 (-53, -47)	-36 (-39, -33)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
REPATHA every 2 weeks vs. Ezetimibe 10 mg daily (Background statin: atorvastatin 10 mg or 80 mg)				
Ezetimibe 10 mg daily (n = 112)	-17	-16	-14	-12
REPATHA 140 mg every 2 weeks [†] (n = 219)	-63	-52	-49	-36
Mean difference from Ezetimibe (95% CI)	-45 (-52, -39)	-36 (-41, -31)	-35 (-40, -31)	-24 (-28, -20)
REPATHA once monthly vs. Ezetimibe 10 mg daily (Background statin: atorvastatin 10 mg or 80 mg)				
Ezetimibe 10 mg daily (n = 109)	-19	-16	-11	-12
REPATHA 420 mg once monthly (n = 220)	-59	-50	-46	-34
Mean difference from Ezetimibe (95% CI)	-41 (-47, -35)	-35 (-40, -29)	-34 (-39, -30)	-22 (-26, -19)

Estimates based on a multiple imputation model that accounts for treatment adherence.

[†]140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

Figure 3. Effect of REPATHA on LDL-C in Patients with Hyperlipidemia when Combined with Statins (Mean % Change from Baseline to Week 12 in LAPLACE-2)



Estimates based on a multiple imputation model that accounts for treatment adherence

Error bars indicate 95% confidence intervals

Study 3 (DESCARTES, NCT01516879) was a multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 901 patients with hyperlipidemia who received protocol-determined background lipid-lowering therapy of a cholesterol-lowering diet either alone or in addition to atorvastatin (10 mg or 80 mg daily) or the combination of atorvastatin 80 mg daily with ezetimibe. After stabilization on background therapy, patients were randomly assigned to the addition of placebo or REPATHA 420 mg administered subcutaneously once monthly. Overall, the mean age at baseline was 56 years (range: 25 to 75 years), 23% were ≥ 65 years, 52% women, 80% White, 8% Black,

and 6% Asian; 6% identified as Hispanic or Latino ethnicity. After stabilization on the assigned background therapy, the mean baseline LDL-C ranged between 90 and 117 mg/dL across the four background therapy groups.

In these patients with hyperlipidemia on a protocol-determined background therapy, the difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -55% (95% CI: -60%, -50%; $p < 0.0001$) (Table 5 and Figure 4). For additional results see Table 5.

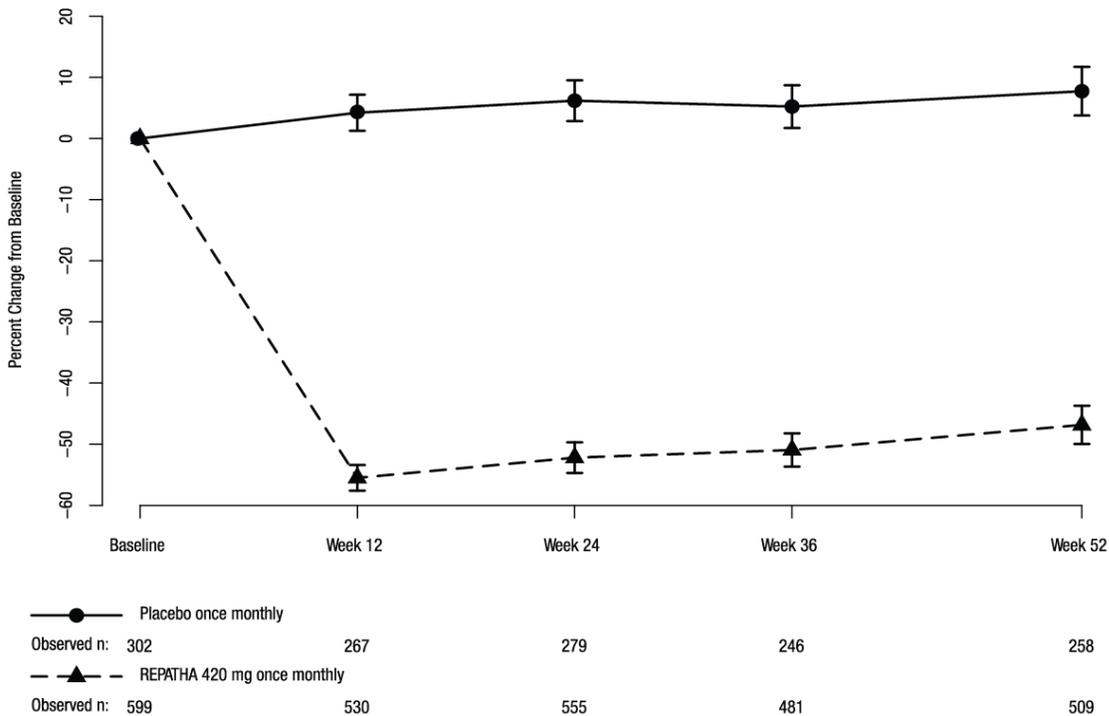
Table 5. Effect of REPATHA on Lipid Parameters in Patients with Hyperlipidemia* (Mean % Change from Baseline to Week 52 in DESCARTES)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 302)	8	8	2	5
REPATHA 420 mg once monthly (n = 599)	-47	-39	-38	-26
Mean difference from placebo (95% CI)	-55 (-60, -50)	-46 (-50, -42)	-40 (-44, -37)	-31 (-34, -28)

Estimates based on a multiple imputation model that accounts for treatment adherence

*Prior to randomization, patients were stabilized on background therapy consisting of a cholesterol-lowering diet either alone or in addition to atorvastatin (10 mg or 80 mg daily) or the combination of atorvastatin 80 mg daily with ezetimibe.

Figure 4. Effect of REPATHA 420 mg Once Monthly on LDL-C in Patients with Hyperlipidemia in DESCARTES



Estimates based on a multiple imputation model that accounts for treatment adherence

Error bars indicate 95% confidence intervals

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Study 4 (MENDEL-2, NCT01763827) was a multicenter, double-blind, randomized, placebo- and active-controlled, 12-week trial that included 614 patients with hyperlipidemia who were not taking lipid-lowering therapy at baseline. Patients were randomly assigned to receive subcutaneous injections of REPATHA 140 mg every 2 weeks, REPATHA 420 mg once monthly, or placebo for 12 weeks. Blinded administration of ezetimibe was also included as an active control. Overall, the mean age at baseline was 53 years (range: 20 to 80 years), 18% were ≥ 65 years old, 66% were women, 83% White, 7% Black, and 9% Asian; 11% identified as Hispanic or Latino ethnicity. The mean baseline LDL-C was 143 mg/dL.

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -55% (95% CI: -60%, -50%; $p < 0.0001$) and -57% (95% CI: -61%, -52%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. The difference between REPATHA and ezetimibe in mean percent change in LDL-C from baseline to Week 12 was -37% (95% CI: -42%, -32%; $p < 0.0001$) and -38% (95% CI: -42%, -34%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 6.

Table 6. Effect of REPATHA on Lipid Parameters in Patients with Hyperlipidemia (Mean % Change from Baseline to Week 12 in MENDEL-2)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo every 2 weeks (n = 76)	1	0	1	0
Ezetimibe 10 mg daily (n = 77)	-17	-14	-13	-10
REPATHA 140 mg every 2 weeks [†] (n = 153)	-54	-47	-44	-34
Mean difference from placebo (95% CI)	-55 (-60, -50)	-47 (-52, -43)	-45 (-50, -41)	-34 (-37, -30)
Mean difference from Ezetimibe (95% CI)	-37 (-42, -32)	-33 (-37, -29)	-32 (-36, -27)	-23 (-27, -20)
Placebo once monthly (n = 78)	1	2	2	0
Ezetimibe 10 mg daily (n = 77)	-18	-16	-13	-12
REPATHA 420 mg once monthly (n = 153)	-56	-49	-46	-35
Mean difference from placebo (95% CI)	-57 (-61, -52)	-51 (-54, -47)	-48 (-52, -44)	-35 (-38, -32)
Mean difference from Ezetimibe (95% CI)	-38 (-42, -34)	-32 (-36, -29)	-33 (-36, -29)	-23 (-26, -20)

Estimates based on a multiple imputation model that accounts for treatment adherence

[†]140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

Study 5 (RUTHERFORD-2, NCT01763918) was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 329 patients with heterozygous familial hypercholesterolemia (HeFH) on statins with or without other lipid-lowering therapies. Patients were randomized to receive subcutaneous injections of REPATHA 140 mg every two weeks, 420 mg once monthly, or placebo. HeFH was diagnosed by the Simon Broome criteria (1991). In Study 5, 38% of patients had clinical atherosclerotic cardiovascular disease. The mean age at baseline was 51 years (range: 19 to 79 years), 15% of the patients were ≥ 65 years old, 42% were women, 90% were White, 5% were Asian, and 1% were Black. The average LDL-C at baseline was 156 mg/dL with 76% of the patients on high-intensity statin therapy.

The differences between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -61% (95% CI: -67%, -55%; $p < 0.0001$) and -60% (95% CI: -68%, -52%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 7 and Figure 5.

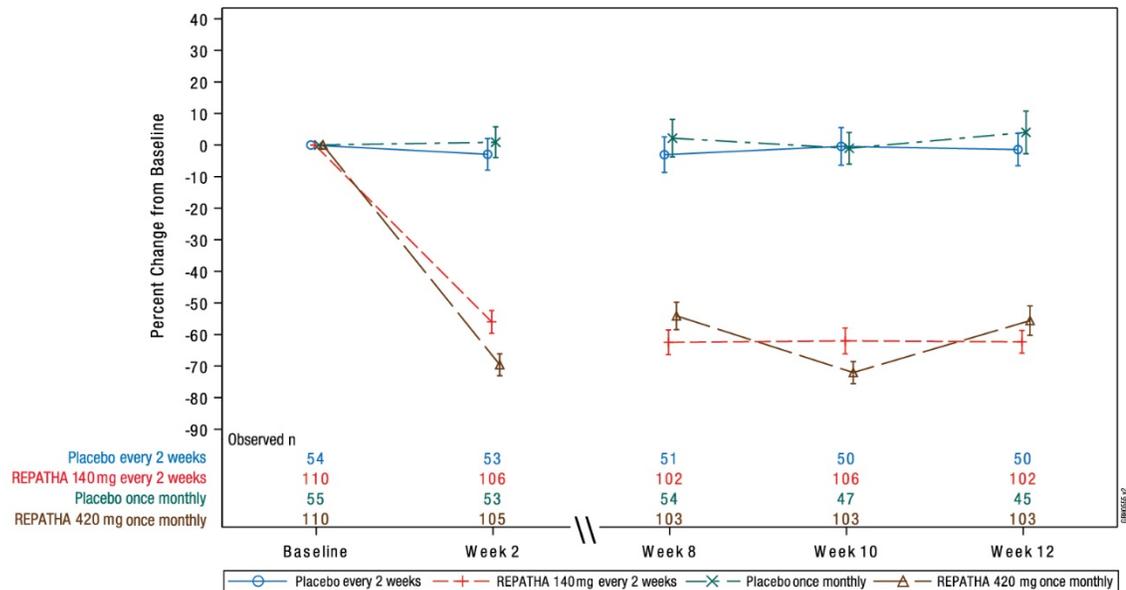
Table 7. Effect of REPATHA on Lipid Parameters in Patients with HeFH (Mean % Change from Baseline to Week 12 in RUTHERFORD-2)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo every 2 weeks (n = 54)	-1	-1	-1	-2
REPATHA 140 mg every 2 weeks [†] (n = 110)	-62	-56	-49	-42
Mean difference from placebo (95% CI)	-61 (-67, -55)	-54 (-60, -49)	-49 (-54, -43)	-40 (-45, -36)
Placebo once monthly (n = 55)	4	4	4	2
REPATHA 420 mg once monthly (n = 110)	-56	-49	-44	-37
Mean difference from placebo (95% CI)	-60 (-68, -52)	-53 (-60, -46)	-48 (-55, -41)	-39 (-45, -33)

Estimates based on a multiple imputation model that accounts for treatment adherence

[†]140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

Figure 5. Effect of REPATHA on LDL-C in Patients with HeFH (Mean % Change from Baseline to Week 12 in RUTHERFORD-2)



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

Estimates based on a multiple imputation model that accounts for treatment adherence

Error bars indicate 95% confidence intervals

14.3 Homozygous Familial Hypercholesterolemia (HoFH)

Study 6 (TESLA, NCT01588496) was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with homozygous familial

hypercholesterolemia (HoFH). In this trial, 33 patients received subcutaneous injections of 420 mg of REPATHA once monthly and 16 patients received placebo as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe). The mean age at baseline was 31 years, 49% were women, 90% White, 4% were Asian, and 6% other. The trial included 10 adolescents (ages 13 to 17 years), 7 of whom received REPATHA. The mean LDL-C at baseline was 349 mg/dL with all patients on statins (atorvastatin or rosuvastatin) and 92% on ezetimibe. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents.

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -31% (95% CI: -44%, -18%; p < 0.0001). For additional results see Table 8.

Patients known to have two LDL-receptor negative alleles (little to no residual function) did not respond to REPATHA.

Table 8. Effect of REPATHA on Lipid Parameters in Patients with HoFH (Mean % Change from Baseline to Week 12 in TESLA)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 16)	9	8	4	8
REPATHA 420 mg once monthly (n = 33)	-22	-20	-17	-17
Mean difference from placebo (95% CI)	-31 (-44, -18)	-28 (-41, -16)	-21 (-33, -9)	-25 (-36, -14)

Estimates based on a multiple imputation model that accounts for treatment adherence

16 HOW SUPPLIED/STORAGE AND HANDLING

REPATHA is a sterile, clear to opalescent, colorless to pale yellow solution for subcutaneous administration supplied in a single-use prefilled syringe, a single-use prefilled SureClick® autoinjector, or a single-use Pushtronex® system (on-body infusor with prefilled cartridge). Each single-use prefilled syringe or single-use prefilled SureClick® autoinjector of REPATHA is designed to deliver 1 mL of 140 mg/mL solution. Each single-use Pushtronex® system (on-body infusor with prefilled cartridge) is designed to deliver 420 mg evolocumab in 3.5 mL solution.

140 mg/mL single-use prefilled syringe	1 pack	NDC 55513-750-01
140 mg/mL single-use prefilled SureClick® autoinjector	1 pack	NDC 55513-760-01
140 mg/mL single-use prefilled SureClick® autoinjector	2 pack	NDC 55513-760-02
140 mg/mL single-use prefilled SureClick® autoinjector	3 pack	NDC 55513-760-03
420 mg/3.5 mL single-use Pushtronex® system (on-body infusor with prefilled cartridge)	1 pack	NDC 55513-770-01

Pharmacy

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

For Patients/Caregivers

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. Alternatively, REPATHA can be kept at room temperature at 68°F to 77°F (20°C to 25°C) in the original carton; however, under these conditions, REPATHA must be used within 30 days. If not used within the 30 days, discard REPATHA.

Protect REPATHA from direct light and do not expose to temperatures above 25°C (77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling [**Patient Information** and **Instructions for Use (IFU)**] before the patient starts using REPATHA, and each time the patient gets a refill as there may be new information they need to know.

Inform patients that serious hypersensitivity reactions (e.g., angioedema) have been reported in patients treated with REPATHA. Advise patients on the symptoms of hypersensitivity reactions and instruct them to discontinue REPATHA and seek medical attention promptly, if such symptoms occur.

Provide guidance to patients and caregivers on proper subcutaneous administration technique, including aseptic technique, and how to use the single-use prefilled autoinjector, single-use prefilled syringe, or single-use on-body infusor with prefilled cartridge correctly (see **Instructions for Use** leaflet). Inform patients that it may take up to 15 seconds to administer REPATHA using the single-use prefilled autoinjector or single-use prefilled syringe and about 9 minutes to administer REPATHA using the single-use on-body infusor with prefilled cartridge.

Advise latex-sensitive patients that the following components contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex: the needle cover of the glass single-use prefilled syringe and the single-use prefilled autoinjector.

The single-use on-body infusor with prefilled cartridge is not made with natural rubber latex.

For more information about REPATHA, go to www.REPATHA.com or call 1-844-REPATHA (1-844-737-2842).



REPATHA® (evolocumab)

Manufactured by:

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

U.S. License Number 1080

Patent: <http://pat.amgen.com/repatha/>

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Patient Information
REPATHA® (ri-PATH-a)
(evolocumab)
injection, for subcutaneous use

What is REPATHA?

REPATHA is an injectable prescription medicine used:

- in adults with cardiovascular disease to reduce the risk of heart attack, stroke, and certain types of heart surgery.
- along with diet alone or together with other cholesterol-lowering medicines in adults with high blood cholesterol levels called primary hyperlipidemia (including a type of high cholesterol called heterozygous familial hypercholesterolemia) to reduce low density lipoprotein (LDL) or bad cholesterol.
- along with diet and other LDL-lowering medicine in people with a type of high cholesterol called homozygous familial hypercholesterolemia (HoFH), who need additional lowering of LDL cholesterol.

It is not known if REPATHA is safe and effective in children with HoFH who are younger than 13 years of age or in children who do not have HoFH.

Who should not use REPATHA?

Do not use REPATHA if you are allergic to evolocumab or to any of the ingredients in REPATHA. See the end of this leaflet for a complete list of ingredients in REPATHA.

What should I tell my healthcare provider before using REPATHA?

Before you start using REPATHA, tell your healthcare provider about all your medical conditions, including if you:

- are allergic to rubber or latex. The needle covers on the single-use prefilled syringes and within the needle caps on the single-use prefilled SureClick® autoinjectors contain dry natural rubber. The single-use Pushtonex® system (on-body infusor with prefilled cartridge) is not made with natural rubber latex.
- are pregnant or plan to become pregnant. It is not known if REPATHA will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking REPATHA.

Pregnancy Registry. There is a pregnancy registry for women who take REPATHA during pregnancy. The purpose of this registry is to collect information about your health and your baby's health. You can talk to your healthcare provider or contact 1-877-311-8972 or go to <https://mothertobaby.org/ongoing-study/repatha/> to enroll in this registry or get more information.

- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take REPATHA or breastfeed.

Tell your healthcare provider or pharmacist about any prescription and over-the-counter medicines, vitamins, or herbal supplements you take.

How should I use REPATHA?

- **See the detailed “Instructions for Use” that comes with this patient information about the right way to prepare and give REPATHA.**
- Use REPATHA exactly as your healthcare provider tells you to use it.
- REPATHA is given under the skin (subcutaneously), every 2 weeks or 1 time each month.
- REPATHA comes as a single-use (1 time) prefilled autoinjector (SureClick® autoinjector), as a single-use prefilled syringe or as a single-use Pushtonex® system (on-body infusor with prefilled cartridge). Your healthcare provider will prescribe the type and dose that is best for you.
- If your healthcare provider prescribes you the monthly dose, you may use:
 - a single-use on-body infusor with prefilled cartridge to give the injection over 9 minutes, or
 - 3 separate injections in a row, using a different single-use prefilled syringe or single-use prefilled autoinjector for each injection. Give all of these injections within 30 minutes.
- If your healthcare provider decides that you or a caregiver can give REPATHA, you or your caregiver should receive training on the right way to prepare and inject REPATHA. **Do not** try to inject REPATHA until you have been shown the right way by your healthcare provider or nurse.
- **Do not** inject REPATHA together with other injectable medicines at the same injection site.
- Always check the label of your single-use prefilled autoinjector, single-use prefilled syringe, or single-use on-body infusor with prefilled cartridge to make sure you have the correct medicine and the correct dose of REPATHA before each injection.
- If you forget to use REPATHA or are not able to take the dose at the regular time, inject your missed dose as soon as you remember, as long as it is within 7 days of the missed dose.
 - If it is more than 7 days from the missed dose and you are using the every-2-week dose, inject the next dose based

on your original schedule. This will put you back on your original schedule.

- If it is more than 7 days from the missed dose and you are using the 1 time each-month dose, inject the dose and start a new schedule using this date.

If you are not sure when to take REPATHA after a missed dose, ask your healthcare provider or pharmacist.

- If your healthcare provider has prescribed REPATHA along with other cholesterol-lowering medicines, follow instructions from your healthcare provider. Read the patient information for those medicines.
- If you use more REPATHA than you should, talk to your healthcare provider or pharmacist.
- **Do not** stop using REPATHA without talking with your healthcare provider. If you stop using REPATHA, your cholesterol levels can increase.

What are possible side effects of REPATHA?

REPATHA can cause serious side effects including:

- **Serious allergic reactions.** Some people taking REPATHA have had serious allergic reactions. Stop taking REPATHA and call your healthcare provider or seek emergency medical help right away if you have any of these symptoms:
 - trouble breathing or swallowing
 - raised bumps (hives)
 - rash, or itching
 - swelling of the face, lips, tongue, throat, or arms

The most common side effects of REPATHA include: runny nose, sore throat, symptoms of the common cold, flu or flu-like symptoms, back pain, high blood sugar levels (diabetes) and redness, pain, or bruising at the injection site.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of REPATHA. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of REPATHA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use REPATHA for a condition for which it was not prescribed. **Do not** give REPATHA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about REPATHA that is written for healthcare professionals.

What are the ingredients in REPATHA?

- Active Ingredient: evolocumab
- Inactive Ingredients: proline, glacial acetic acid, polysorbate 80, water for injection, and sodium hydroxide.

Manufactured by: Amgen Inc. One Amgen Center Drive, Thousand Oaks, California 91320-1799.

U.S. License Number 1080

Patent: <http://pat.amgen.com/repatha/>

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: