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

----------INDICATIONS AND USAGE----------
REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and:
- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). (1.1)
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. (1.2)

Limitations of Use
- The effect of REPATHA on cardiovascular morbidity and mortality has not been determined. (1.3)

----------DOSAGE AND ADMINISTRATION----------
- Administer by subcutaneous injection (2.1)
- Primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH: 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)
- To administer 420 mg, give 3 REPATHA injections consecutively within 30 minutes. (2.2)
- See Dosage and Administration for important administration instructions. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 140 mg/mL in a single-use prefilled syringe (3)
- Injection: 140 mg/mL in a single-use prefilled SureClick® autoinjector (3)

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

----------WARNINGS AND PRECAUTIONS----------
Allergic Reactions: 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 (>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)

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: 8/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Primary Hyperlipidemia

REPATHA™ is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

1.2 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.

1.3 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended subcutaneous dosage of REPATHA in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD is either 140 mg every 2 weeks OR 420 mg once monthly. 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.

If an every 2 week or once monthly dose is missed, instruct the patient to:

- Administer REPATHA as soon as possible if there are more than 7 days until the next scheduled dose, or,
- Omit the missed dose and administer the next dose according to the original schedule.

2.2 Important Administration Instructions

- To administer the 420 mg dose, give 3 REPATHA injections consecutively within 30 minutes.

- 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. Do not warm in any other way. Alternatively, for patients and caregivers, REPATHA can be kept at room temperature (up to 25°C (77°F)) 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 by subcutaneous injection into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated using a single-use pre-filled syringe or single-use pre-filled autoinjector.

- Do not co-administer REPATHA with other injectable drugs at the same injection site.

- Rotate the injection site with each injection.

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

4 CONTRAINDICATIONS

REPATHA is contraindicated in patients with a history of a serious hypersensitivity reaction to REPATHA *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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.

6 ADVERSE REACTIONS

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

- 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 Patients with Primary Hyperlipidemia and in Patients with Heterozygous Familial Hypercholesterolemia

REPATHA is not indicated for use in patients without familial hypercholesterolemia or atherosclerotic CVD *[see Indications and Usage (1.1)]*.

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% were White, 6% were Black, 8% were Asians, and 2% were other races.

Adverse Reactions in a 52-Week Controlled Trial
In a 52-week, double-blind, randomized, placebo-controlled trial (Study 2), 599 patients received 420 mg of REPATHA subcutaneously once monthly *[see Clinical Studies (14.1)]*. The mean age was 56 years (range: 22 to 75 years), 23% were older than 65 years, 52% were women, 80% White, 8% Black, 6% Asian, and 6% Hispanic. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients in Study 2, 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 Study 2

	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
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% were women, 85% White, 5% Black, 9% Asian, and 5% Hispanic. 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 Studies

	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 (Study 2) 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 4.6% 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%).

Neurocognitive Events
In placebo-controlled trials, neurocognitive events were reported in less than or equal to 0.2% in REPATHA-treated and placebo-treated patients.

Low LDL-C Levels
In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1609 patients treated with REPATHA had at least one LDL-C value < 25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and REPATHA dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C

were not identified in these trials, the long-term effects of very low levels of LDL-C induced by REPATHA are unknown.

Musculoskeletal Events
Musculoskeletal adverse reactions were reported in 14.3% of REPATHA-treated patients and 12.8% of placebo-treated patients. The most common adverse reactions that occurred at a rate greater than placebo were back pain (3.2% versus 2.9% for REPATHA and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).

Adverse Reactions in Patients with Homozygous Familial Hypercholesterolemia
In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (Study 4), 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, 88% were White, 3% Asian, and 9% 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 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, 0.1% of patients treated with at least one dose of REPATHA tested positive for binding antibody development. 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.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of 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 with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 studies, 1420 patients treated with REPATHA were ≥ 65 years old and 171 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 mild to moderate renal impairment. No data are available in patients with severe 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 injection. 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.

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) µg/mL and AUC_{last} mean (SD) of 188 (98.6) day•µg/mL. Administration of the 420 mg dose in healthy volunteers resulted in a C_{max} mean (SD) of 59.0 (17.2) µg/mL and AUC_{last} mean (SD) of 924 (346) day•µg/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. Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) have not been studied.

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 Primary Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease

Study 1 was a multicenter, double-blind, randomized controlled 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 296 patients with atherosclerotic CVD who received REPATHA or placebo as add-on therapy to daily doses of atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg. Among these patients, the mean age at baseline was 63 years (range: 32 to 80 years), 45% were ≥ 65 years old, 33% were women, 98% were White, 2% were Black, < 1% were Asian and 5% were Hispanic or Latino. After 4 weeks of statin therapy, the mean baseline LDL-C was 108 mg/dL.

In these patients with atherosclerotic CVD who were on maximum-dose statin therapy, the difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -71%

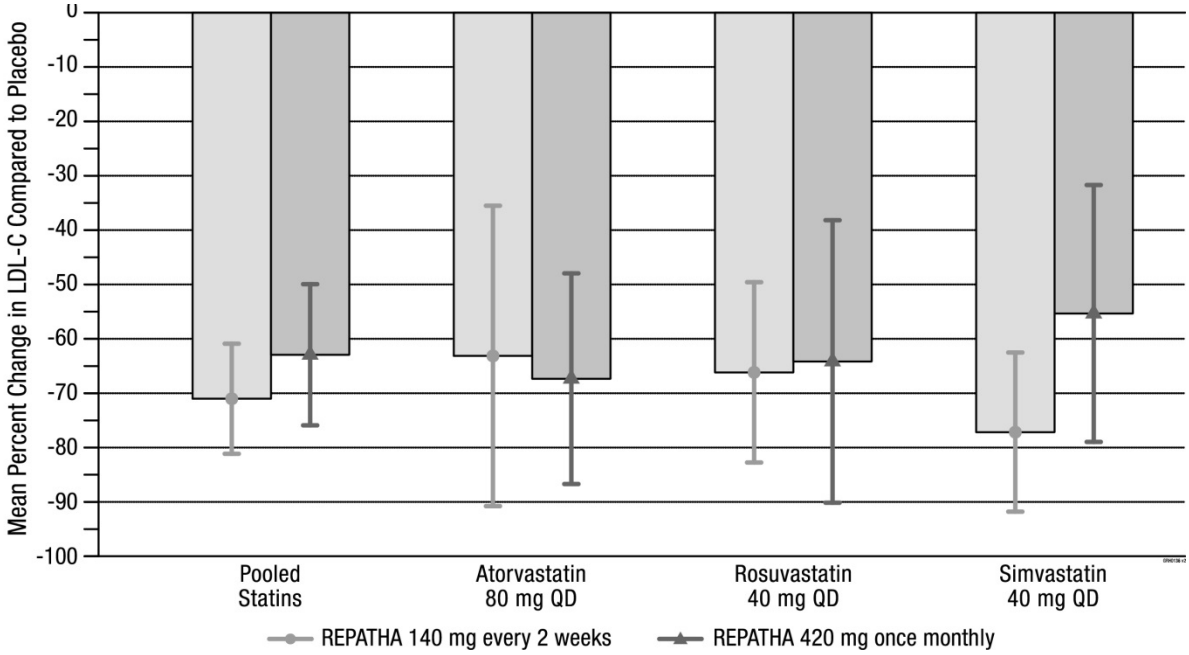
(95% CI: -81%, -61%; p < 0.0001) and -63% (95% CI: -76%, -50%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 3 and Figure 1.

Table 3. Effect of REPATHA on Lipid Parameters in Patients with Atherosclerotic CVD on Atorvastatin 80 mg, Rosuvastatin 40 mg, or Simvastatin 40 mg (Mean % Change from Baseline to Week 12 in Study 1)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo every 2 weeks (n=42)	7	2	5	4
REPATHA 140 mg every 2 weeks† (n=105)	-64	-56	-49	-38
Mean difference from placebo (95% CI)	-71 (-81, -61)	-58 (-67, -49)	-55 (-62, -47)	-42 (-48, -36)
Placebo once monthly (n=44)	5	5	3	3
REPATHA 420 mg once monthly† (n=105)	-58	-47	-46	-32
Mean difference from placebo (95% CI)	-63 (-76, -50)	-52 (-63, -41)	-49 (-58, -39)	-36 (-43, -28)

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 1. Effect of REPATHA on LDL-C in Patients with Atherosclerotic CVD When Combined with Statins (Mean % Change from Baseline to Week 12 in Study 1)



Estimates based on a multiple imputation model that accounts for treatment adherence
Error bars indicate 95% confidence intervals

Study 2 was a multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 139 patients with atherosclerotic CVD who received protocol-determined background lipid-lowering

therapy of atorvastatin 80 mg daily with or without ezetimibe 10 mg daily. After stabilization on background therapy, patients were randomly assigned to the addition of placebo or REPATHA 420 mg administered subcutaneously once monthly. Among these patients, the mean age at baseline was 59 years (range, 35 to 75 years), 25% were ≥ 65 years, 40% were women, 80% were White, 3% were Black, 5% were Asian, and < 1% were Hispanic or Latino. After stabilization on the assigned background therapy, the mean baseline LDL-C was 105 mg/dL.

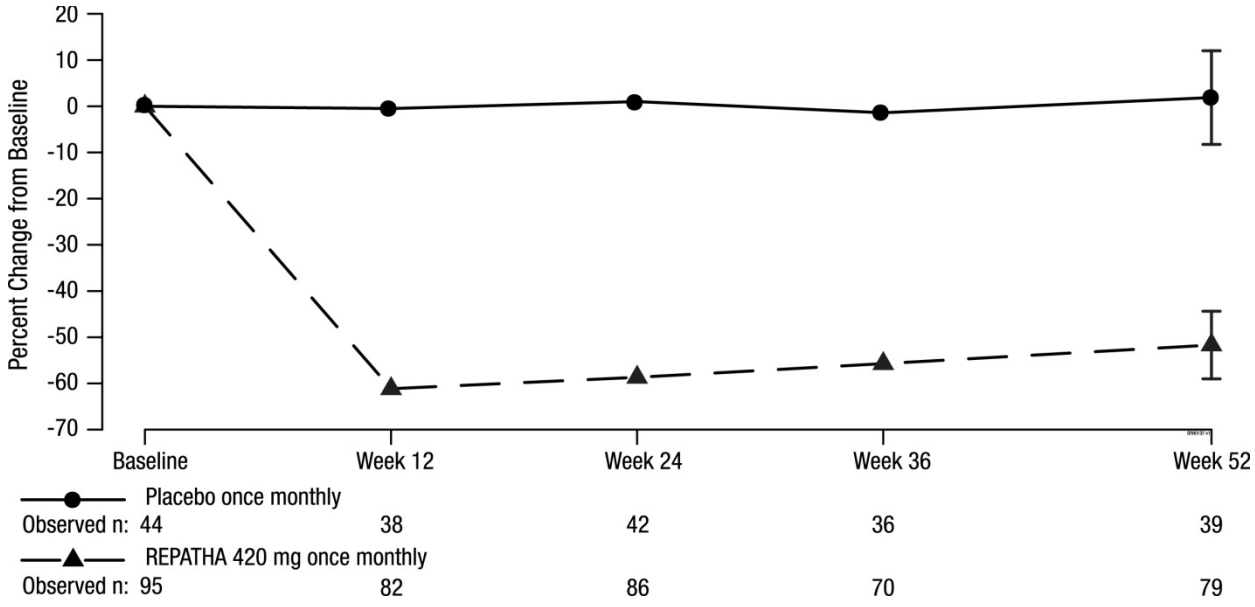
In these patients with atherosclerotic CVD on maximum-dose atorvastatin therapy with or without ezetimibe, the difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -54 % (95% CI: -65%, -42%; p <0.0001) (Table 4 and Figure 2). For additional results see Table 4.

Table 4. Effect of REPATHA on Lipid Parameters in Patients with Atherosclerotic CVD on Atorvastatin 80 mg with or without Ezetimibe 10 mg daily (Mean % Change from Baseline to Week 52 in Study 2)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n=44)	2	3	0	3
REPATHA 420 mg once monthly (n=95)	-52	-41	-40	-28
Mean difference from placebo (95% CI)	-54 (-65, -42)	-44 (-56, -32)	-40 (-50, -30)	-31 (-39, -24)

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

Figure 2: Effect of REPATHA 420 mg Once Monthly on LDL-C in Patients with Atherosclerotic CVD on Atorvastatin 80 mg with or without Ezetimibe 10 mg Daily



Estimates based on a multiple imputation model that accounts for treatment adherence
Error bars indicate 95% confidence intervals

14.2 Heterozygous Familial Hypercholesterolemia (HeFH)

Study 3 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 3, 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.

In these patients with HeFH on statins with or without other lipid lowering therapies, 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 5.

Table 5: Effect of REPATHA on Lipid Parameters in Patients with HeFH (Mean % Change from Baseline to Week 12 in Study 3)

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

14.3 Homozygous Familial Hypercholesterolemia

Study 4 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.

In these patients with HoFH, 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 6.

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

Table 6: Effect of REPATHA on Lipid Parameters in Patients with HoFH (Mean % Change from Baseline to Week 12 in Study 4)

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 injection supplied in a single-use pre-filled syringe or a single-use prefilled SureClick® autoinjector. Each single-use prefilled syringe or single-use prefilled SureClick® autoinjector of REPATHA is designed to deliver 1 mL of 140 mg/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

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

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

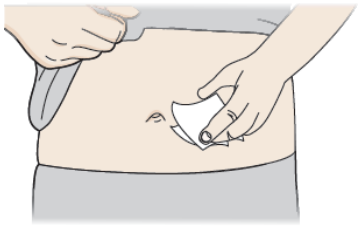
Protect REPATHA from direct light and do not expose to temperatures above 25°C (77°F).

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.

Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the pre-filled autoinjector or pre-filled syringe correctly (see **Instructions for Use** leaflet). Inform patients that it may take up to 15 seconds to inject REPATHA.

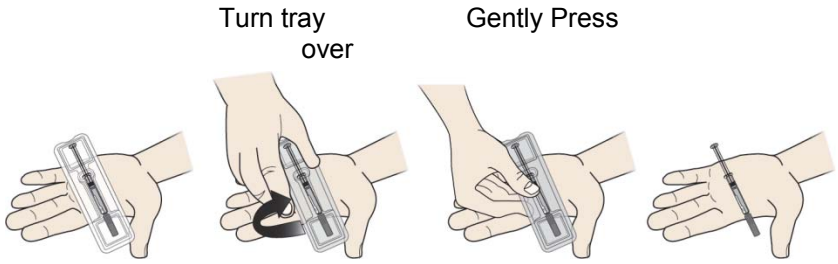
1 D	Clean your injection site.



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

Do not touch this area of skin again before injecting.

1 E	Remove prefilled syringe from tray.



To remove:

- Peel paper off of tray.
- Place the tray on your hand.
- Turn the tray over and gently press the middle of the tray's back to release the syringe into your palm.
- If prefilled syringe does not release from tray, gently press on back of tray

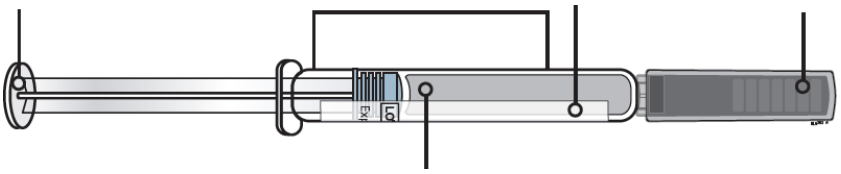
Do not pick up or pull the prefilled syringe by the plunger rod or gray needle cap. This could damage the syringe.

Do not remove the gray needle cap from the prefilled syringe until you are ready to inject.

Always hold the prefilled syringe by the syringe barrel.

1 F	Check the medicine and syringe.

Plunger rod | Syringe barrel | Syringe label with expiration date | Gray needle cap on



Medicine

Always hold the prefilled syringe by the syringe barrel.
Check that:

- the name Repatha appears on the prefilled syringe label.
- the medicine in the prefilled syringe is clear and colorless to slightly yellow.
- the expiration date on the prefilled syringe has not passed. If the expiration date has passed, **do not** use the prefilled syringe.

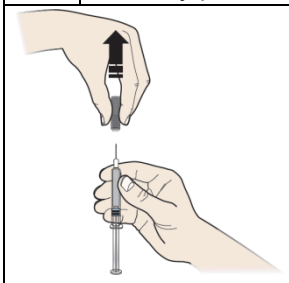
Do not use the prefilled syringe if any part of the prefilled syringe appears cracked or broken.

Do not use the prefilled syringe if the gray needle cap is missing or not securely attached.

Do not use the prefilled syringe if the medicine is cloudy or discolored or contains particles.

In any above cases, use a new prefilled syringe and call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

Step 2: Get ready	
2 A	Carefully pull the gray needle cap straight out and away from your body.



It is normal to see a drop of medicine at the end of the needle.

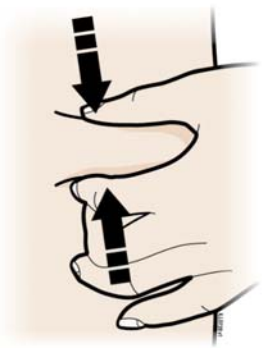
Place the cap in the sharps disposal container right away.

Do not twist or bend the gray needle cap. This can damage the needle.

Do not put the gray needle cap back onto the prefilled syringe.

Do not try to remove any air bubbles in the syringe before the injection.

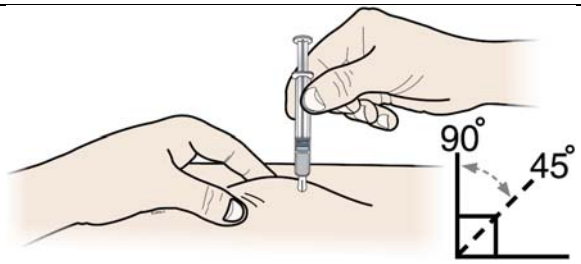
2 B	**Pinch** your injection site to create a firm surface.



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

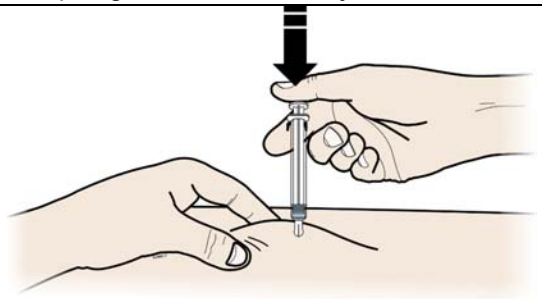
It is important to keep the skin pinched while injecting.

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

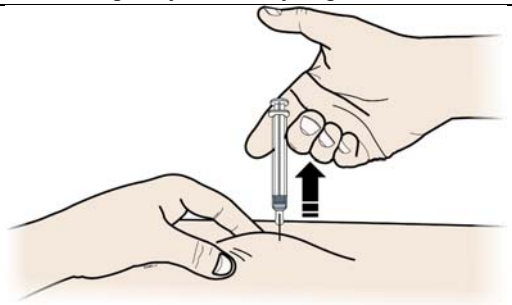


Do not place your finger on the plunger rod while inserting the needle.

3 B	Using slow and constant pressure, **push** the plunger rod all the way down until the syringe is empty. You may have to push harder on the plunger than for other injectable medicines.



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



Do not put the gray needle cap back onto the used syringe.

Step 4: Finish	
4 A	Place the used syringe in a sharps disposal container right away.

Do not reuse the used syringe.

Do not use any medicine that is left in the used syringe.

- Put the used syringe in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the syringe in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - o made of a heavy-duty plastic,
  - o can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - o upright and stable during use,
  - o leak-resistant, and
  - o properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

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

4 B	Check the injection site.
	If there is blood, press a cotton ball or gauze pad on your injection site. Apply an adhesive bandage if needed. **Do not** rub the injection site.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Amgen Inc.
Thousand Oaks, CA 91320-1799

<part number> Issued: 08/2015 v1

Welcome!
The Repatha single-use prefilled syringe contains one 140 mg dose of Repatha. Your healthcare provider has prescribed Repatha as part of your treatment. Your healthcare provider will tell you how much Repatha you need and how often it should be injected. **Each Repatha prefilled syringe can only be used one time.** Side 2 of this sheet contains information on how to give an injection of Repatha. It is important that you do not try to give the injection unless you have received training from your healthcare provider. **Please read all of the instructions on side 2 before using the Repatha prefilled syringe.**