PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]REPATHA®

(evolocumab)

Solution for Subcutaneous Injection

140 mg in 1.0 mL (140 mg/mL)

420 mg in 3.5 mL (120 mg/mL)

anti-Proprotein Convertase Subtilisin/Kexin Type 9 (anti-PCSK9) Monoclonal Antibody

Amgen Canada Inc.
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PrREPATHA®

(evolocumab)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Solution Prefilled syringe* and autoinjector: 140 mg/mL Automated mini-doser with prefilled cartridge: 120 mg/mL	proline, glacial acetic acid (acetate), polysorbate 80, sodium hydroxide, water for injection *For a complete listing see Dosage Forms, Composition and Packaging section.*

* Prefilled syringes are not available in Canada.

DESCRIPTION

REPATHA (evolocumab) is a fully human immunoglobulin G2 (IgG2) monoclonal antibody that has high affinity binding to Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). Evolocumab is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells. The approximate molecular weight of evolocumab is 144 kDa.

INDICATIONS AND CLINICAL USE

Prevention of Cardiovascular Events

REPATHA is indicated as an adjunct to diet and standard of care therapy (including moderate- to high-intensity statin therapy alone or in combination with other lipid-lowering therapy), to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adult patients with atherosclerotic cardiovascular disease (see **CLINICAL TRIALS**).

Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

REPATHA is indicated for the reduction of elevated low density lipoprotein cholesterol (LDL-C) in adult patients with primary hyperlipidemia (including heterozygous familial hypercholesterolemia):

- as an adjunct to diet and statin therapy, with or without other lipid-lowering therapies, in patients who require additional lowering of LDL-C
- as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated

Homozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in adult patients and adolescent patients aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Geriatrics (≥ 65 years of age):

Of the 18,546 patients treated with REPATHA in double-blinded clinical studies, 7656 (41.3%) were ≥ 65 years of age, while 1500 (8.1%) were ≥ 75 years of age. No overall differences in safety or efficacy were observed between these patients and younger patients (see **WARNINGS AND PRECAUTIONS, *Special Populations*, Geriatrics**).

Pediatrics (< 18 years of age):

REPATHA has not been studied in pediatric patients < 18 years of age with primary hyperlipidemia.

REPATHA has not been studied in pediatric patients <12 years of age with homozygous familial hypercholesterolemia (see **WARNINGS AND PRECAUTIONS, *Special Populations*, Pediatrics**).

CONTRAINDICATIONS

- Patients who are hypersensitive to REPATHA or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- For the lipid lowering therapies such as statin or other lipid lowering therapies used in combination with REPATHA, see the **CONTRAINDICATIONS** section of the product monographs for those medications.

WARNINGS AND PRECAUTIONS

General

Concomitant Lipid Lowering Therapies

When using REPATHA in combination with statins or other lipid lowering therapies (e.g., ezetimibe), the prescriber should refer to the **WARNINGS AND PRECAUTIONS** sections of the product monographs for those medications.

Hypersensitivity in Latex-sensitive patients

The needle cap of the prefilled syringe* and the autoinjector contains dry natural rubber, which is a derivative of latex. This may cause an allergic reaction in latex-sensitive patients. There is no dry natural rubber in the automated mini-doser with prefilled cartridge.

Immune

* Prefilled syringes are not available in Canada

Hypersensitivity reactions (e.g., rash, urticaria, angioedema) 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 and treat according to the standard of care and monitor until signs and symptoms resolve (see **ADVERSE REACTIONS**).

Special Populations

Pregnant Women:

No studies have been conducted with REPATHA in pregnant women and relevant data from clinical use are very limited.

Studies in monkeys showed that evolocumab crosses the placental barrier. The serum concentrations in infant monkeys at birth were comparable to the maternal serum. Animal reproduction studies have not shown an effect on embryo-fetal or early postnatal development (see **PART II: TOXICOLOGY**).

Animal studies are not always predictive of human response. Therefore, it is not known whether REPATHA can cause fetal harm when administered to a pregnant woman. For patients being treated for primary hyperlipidemia, REPATHA can be used alone or in combination with other lipid-lowering therapies. Statin product monographs recommend discontinuation when a patient becomes pregnant, therefore REPATHA should also be discontinued (see the ***Special Populations*** section of the product monograph of the statins). For patients being treated for homozygous familial hypercholesterolemia REPATHA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Nursing Women:

There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. A risk to breastfed newborns and infants cannot be excluded. 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.

Fertility:

No data are available on the effect of REPATHA on human fertility. Animal studies did not show any effects on fertility endpoints (see **PART II: TOXICOLOGY**).

Pediatrics (< 18 years of age):

REPATHA has not been studied in pediatric patients < 18 years of age with primary hyperlipidemia.

REPATHA has not been studied in pediatric patients <12 years of age with homozygous familial hypercholesterolemia.

Geriatrics (≥ 65 years of age):

Of the 18,546 patients treated with REPATHA in double-blinded clinical studies, 7656 (41.3%) were ≥ 65 years of age and 1500 (8.1%) were ≥ 75 years of age. No overall differences in safety or efficacy were observed between these patients and younger patients.

Hepatic Impairment:

The safety and efficacy of REPATHA in patients with severe hepatic impairment has not been studied. REPATHA should be used with caution in patients with severe hepatic impairment (Childs-Pugh, Class C).

Renal Impairment:

No dose adjustment is necessary in patients with mild to moderate renal impairment. There is limited experience with REPATHA in patients with severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics, *Special Populations and Conditions*,** Renal Impairment).

Hepatic/Biliary/Pancreatic:

The effects of REPATHA in patients with or at risk of hepatitis C virus (HCV) infection remain uncertain.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of REPATHA was evaluated in approximately 35,141 patients; 18,546 patients received REPATHA, representing 32,231 patient-years of exposure of REPATHA. Adverse events leading to discontinuation of REPATHA occurred infrequently and the overall rate of adverse events leading to discontinuation were similar in patients treated with REPATHA vs. any control group. The most common adverse reactions with REPATHA reported in > 2% of patients and greater than control were diabetes mellitus, nasopharyngitis, upper respiratory tract infection, influenza and injection site reactions (pain, erythema, bruising, swelling and hemorrhage). Rash, urticaria, back pain, arthralgia and nausea have also been reported.

The incidence of serious adverse events were similar in patients treated with REPATHA vs. any control group.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions in the Cardiovascular Outcomes Trial

In a double-blind, randomized, placebo controlled cardiovascular outcomes trial, 13,769 patients received at least one dose of REPATHA and 13,756 received placebo (see **CLINICAL TRIALS, Prevention of Cardiovascular Events**). The mean age of enrolled patients was 62.5 years (range: 40 to 86 years), and 45% were 65 years of age and older. Twenty-five percent (25%) were women, 85% were White, 2% were Black, 10% were Asian, 8% identified as Hispanic. Patients were exposed to REPATHA or placebo for a mean of 24.1 months; 91% of patients were exposed for ≥ 12 months, 54% were exposed for ≥ 24 months, and 5% were exposed for ≥ 36 months.

In general, the safety profile of REPATHA in these patients was consistent with the known safety profile of REPATHA in patients with primary hyperlipidemia (Table 1, Table 2). Serious adverse events were reported in 25% of REPATHA- and placebo-treated patients. Adverse events led to treatment discontinuation in 4.4% of REPATHA-treated patients and 4.2% of placebo-treated patients. Common adverse reactions (≥ 5% of patients in either treatment group) included diabetes mellitus, (REPATHA: 8.8%, placebo: 8.2%), nasopharyngitis (REPATHA: 7.8%, placebo 7.4%) and upper respiratory tract infection (REPATHA 5.1%, placebo: 4.8%).

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 Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

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 events, by system organ class and preferred term, for the 12-week placebo controlled trials occurring in ≥ 1% of patients and occurring more frequently in REPATHA groups (QM dosing and Q2W dosing) than placebo groups (QM dosing and Q2W dosing), are shown in Table 1.

Table 1. Adverse Events Reported by ≥ 1% of REPATHA-treated Patients and More Frequently Than with Placebo by System Organ Class and Preferred Term in the 12-week Studies

System Organ Class Preferred Term	Any Placebo (N = 1224) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 2052) n (%)
Gastrointestinal disorders		
Nausea	15 (1.2)	36 (1.8)
General disorders and administration site conditions		
Fatigue	12 (1.0)	33 (1.6)
Infections and infestations		
Nasopharyngitis	48 (3.9)	82 (4.0)
Upper Respiratory Tract Infection	24 (2.0)	43 (2.1)
Urinary Tract Infection	15 (1.2)	26 (1.3)
Influenza	13 (1.1)	25 (1.2)
Injury, poisoning and procedural complications		
Contusion	6 (0.5)	21 (1.0)
Musculoskeletal and connective tissue disorders		
Back Pain	27 (2.2)	47 (2.3)
Arthralgia	19 (1.6)	37 (1.8)
Muscle Spasms	15 (1.2)	27 (1.3)
Respiratory, thoracic and mediastinal disorders		
Cough	8 (0.7)	25 (1.2)

Includes the following studies: 20090158, 20101154, 20101155, 20110114, 20110115, 20110117, 20110231.
N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab; Q2W = every 2 weeks (subcutaneous) and QM = monthly (subcutaneous)
Coded using MedDRA version 17.0

Adverse Reactions in a 52-Week Controlled Trial

In a 52-week, double-blind, randomized, placebo-controlled trial, REPATHA (420 mg QM (n = 599) was compared to placebo (n = 302) in patients with primary hyperlipidemia on background lipid lowering therapy. 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. The overall incidence of treatment emergent adverse events was comparable between the evolocumab QM (74.8%) and placebo QM (74.2%) treatment groups. Serious adverse events were reported 33 (5.5%) subjects in the evolocumab QM group and 13 (4.3%) in the placebo group. Treatment emergent adverse events leading to discontinuation of the product were 13 (2.2%) vs. 3 (1.0%) in the evolocumab QM group and the placebo QM group, respectively. Adverse events reported in at least 2% of REPATHA-treated patients, and more frequently than in placebo-treated patients are shown in Table 2.

Table 2. Adverse Events Reported by ≥ 2% of REPATHA-treated Patients and More Frequently Than with Placebo by System Organ Class and Preferred Term in the 52-week Study

System Organ Class Preferred Term	Placebo SC QM (N = 302) n (%)	EvoMab 420 mg QM (N = 599) n (%)
Gastrointestinal Disorders		
Diarrhea	8 (2.6)	18 (3.0)
Abdominal Pain Upper	2 (0.7)	13 (2.2)
General Disorders and Administration Site Conditions		
Injection Site Erythema	6 (2.0)	16 (2.7)
Infection and Infestations		
Nasopharyngitis	29 (9.6)	63 (10.5)
Upper Respiratory Tract Infection	19 (6.3)	56 (9.3)
Influenza	19 (6.3)	45 (7.5)
Urinary Tract Infection	11 (3.6)	27 (4.5)
Sinusitis	9 (3.0)	25 (4.2)
Gastroenteritis	6 (2.0)	18 (3.0)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	17 (5.6)	37 (6.2)
Myalgia	9 (3.0)	24 (4.0)
Musculoskeletal Pain	9 (3.0)	20 (3.3)
Osteoarthritis	5 (1.7)	12 (2.0)
Nervous System Disorders		
Headache	11 (3.6)	24 (4.0)
Dizziness	8 (2.6)	22 (3.7)
Respiratory Thoracic and Mediastinal Disorders		
Cough	11 (3.6)	27 (4.5)
Oropharyngeal Pain	4 (1.3)	15 (2.5)
Vascular Disorders		
Hypertension	7 (2.3)	19 (3.2)

N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab; QM = monthly (subcutaneous)
Coded using MedDRA version 17.0

The incidence of treatment emergent adverse events in the homozygous familial hypercholesterolemia population was 12 (36.4%) in the evolocumab 420 mg QM group and 10 (62.5%) in the placebo group. No adverse reactions led to discontinuation during 12-week treatment.

Adverse Reactions in Integrated Phase 2 and Phase 3 Controlled Trials

Allergic Reactions

Hypersensitivity events were reported in 4.5% and 3.9% of REPATHA-treated and control-treated patients, respectively. The most common allergic reactions were rash (1.3% versus 1.2% for REPATHA and control, respectively), eczema (0.6% versus 0.4%), erythema (0.3% versus 0.3%), and urticaria (0.3% versus 0.2%) (see **WARNINGS AND PRECAUTIONS, General,** Immune).

Injection Site Reactions

Injection site reactions have been reported in patients treated with REPATHA (2.2% REPATHA-treated vs. 1.7% control-treated). The most common injection site reactions were pain, bruising, erythema, swelling and hemorrhage. Most of these reactions were mild in severity. The proportions of patients who discontinued treatment due to local injection site reactions were 0.1% in the REPATHA group and 0.1% in the control group. The proportions of patients who experienced recurrent local injection site reactions were 0.51% in the REPATHA group and 0.37% in the control group.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

The adverse reactions described below are from a pool of the 52-week trial and seven 12-week trials that included 2651 patients treated with REPATHA, including 557 exposed for 6 months and 404 exposed for 1 year. The mean and median exposure durations of REPATHA in this pool of eight trials were 20 weeks and 12 weeks, respectively.

The following adverse reactions were reported in the 8 pooled control trials at an incidence of < 1% of patients:

BLOOD AND LYMPHATIC SYSTEM DISORDERS: *Anemia (0.1% placebo vs. 0.6% REPATHA)*

CARDIAC DISORDERS: *Palpitations (0.3% placebo vs. 0.7% REPATHA)*

GASTROINTESTINAL DISORDERS: *Abdominal Pain Upper (0.6% placebo vs. 0.8% REPATHA), Dyspepsia (0.4% placebo vs. 0.6% REPATHA), Abdominal Distension (0.4% placebo vs. 0.5% REPATHA)*

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: *Injection Site Pain (0.6% placebo vs. 0.9% REPATHA), Edema Peripheral (0.7% placebo vs. 0.8% REPATHA), Seasonal Allergy (0.5% placebo vs. 0.6% REPATHA)*

INFECTIONS AND INFESTATIONS: *Cystitis (0.7% placebo vs. 0.8% REPATHA),*

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: *Arthropod Bite (0.1% placebo vs. 0.8% REPATHA),*

INVESTIGATIONS: *Blood Creatine Phosphokinase Increased (0.5% placebo vs. 0.9% REPATHA)*

NERVOUS SYSTEM DISORDERS: *Paresthesia (0.1% placebo vs. 0.6% REPATHA)*

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: *Osteoarthritis (0.5% placebo vs. 0.6% REPATHA), Musculoskeletal Chest Pain (0.4% placebo vs. 0.5% REPATHA) Tendonitis (0.3% placebo vs. 0.5% REPATHA)*

PSYCHIATRIC DISORDERS: *Anxiety (0.2% placebo vs. 0.5% REPATHA)*

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-evolocumab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

In clinical studies, 48 out of 17,992 patients (0.3%) treated with at least one dose of REPATHA tested positive for the development of anti-evolocumab binding antibodies and 39 (0.2%) of these patients had transient antibodies. Of the patients whose sera tested positive for binding antibodies who were further evaluated for neutralizing antibodies, none tested positive for neutralizing antibodies.

The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response or safety of REPATHA.

The detection of anti-drug binding 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 evolocumab with incidence of antibodies to other products may be misleading.

Post-Market Adverse Drug Reactions

In addition to the events listed above, the following adverse reactions have been identified post-market in patients receiving REPATHA:

- Hypersensitivity reactions including angioedema
- Influenza-like illness

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

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

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

None known.

Drug-Lifestyle Interactions

Drug-lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

REPATHA is administered subcutaneously.

REPATHA is intended for patient self-administration after proper training. Administration should be performed by an individual who has been trained to administer the product.

Recommended Dose and Dosage Adjustment

Prevention of Cardiovascular Events and Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The recommended dose for REPATHA is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

One prefilled syringe* (PFS) or prefilled autoinjector (AI) delivers the 140 mg every 2 week dose. One single-use automated mini-doser (AMD) with 3.5 mL prefilled cartridge delivers the 420 mg once monthly dose. Alternatively, 3 prefilled syringes* or 3 prefilled AIs administered consecutively within 30 minutes delivers the 420 mg once monthly dose.

Homozygous Familial Hypercholesterolemia

The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up-titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule. One AMD with prefilled cartridge delivers the 420 mg once monthly dose. Alternatively, three prefilled syringes* or 3 prefilled AIs administered consecutively within 30 minutes deliver the 420 mg once monthly or 420 mg every 2 weeks dose.

*Pre-filled syringes are not available in Canada

Patients with Renal Impairment

There is limited experience in patients with severe or end-stage renal disease (ESRD) receiving hemodialysis. No dosage adjustment may be required in these patient populations. However, REPATHA should be used with caution in patients with severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics,** ***Special Populations and Conditions*****,** Renal Impairment).

Patients with Hepatic Impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment.

Geriatric Patients

No dosage adjustment is necessary in geriatric patients.

Missed Dose

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.

Administration

Prior to subcutaneous administration, allow REPATHA to sit at room temperature up to 25°C for at least 30 minutes for the prefilled syringe* or autoinjector and at least 45 minutes for the automated mini-doser with prefilled cartridge. Do not warm in any other way.

Avoid vigorous shaking of the product.

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

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

Comprehensive instructions for the administration of REPATHA are provided in the Patient Medication Information.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

* Prefilled syringes are not available in Canada

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

REPATHA (evolocumab) is a fully human monoclonal immunoglobulin G2 (IgG2) that binds to Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). REPATHA binds selectively and with high affinity to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein (LDL) receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation therefore increasing the number of LDLR available to clear LDL, thereby lowering serum LDL-C levels.

Pharmacodynamics

REPATHA reduced free PCSK9 in a concentration-related manner. Following a single subcutaneous administration of REPATHA 140 mg or 420 mg, maximum suppression of circulating free PCSK9 occurred within 4 hours, followed by a reduction of LDL-C from baseline reaching nadir by 14 and 21 days, respectively. Free PCSK9 concentrations returned to baseline upon discontinuation of REPATHA.

Pharmacokinetics

Absorption and Distribution

Following a single subcutaneous administration of 140 mg or 420 mg REPATHA, median times to peak serum concentrations (t_{max}) were 3 to 4 days. A greater than dose proportional increase was observed, with a 3.2-fold and 4.9-fold increase in REPATHA maximum concentrations (C_{max}) and total exposure (AUC_{last}), respectively, for a 3-fold increase in dose (140 mg to 420 mg). The absolute bioavailability of REPATHA after SC administration was about 72% as determined by population pharmacokinetics analysis.

Following multiple SC administration of REPATHA at140 mg every 2 weeks (Q2W) or 420 mg monthly (QM), steady state was reached by 12 weeks and an approximate two to three-fold accumulation was observed in trough serum concentrations.

Following a single 420 mg REPATHA intravenous dose, the mean volume of distribution was estimated 3.3 (0.5) L, suggesting REPATHA has limited tissue distribution.

Metabolism and Excretion

REPATHA is expected to be degraded into small peptides and amino acids via catabolic pathways. Two mechanisms of elimination for evolocumab were observed. At low concentrations, the elimination is predominately through saturable binding to target PCSK9, while at higher concentrations the elimination of evolocumab is largely through a non-saturable elimination by endogenous immunoglobulin G (IgG) clearance mechanism.

Following a single 420 mg intravenous dose of REPATHA, the mean (SD) systemic clearance was estimated to be 12 (2) mL/hr. Statins increase the clearance of REPATHA by approximately 20%.

Based on a population pharmacokinetic analysis, the estimated effective half-life of REPATHA in patients is about 11 days for 140 mg SC Q2W and 17 days for 420 mg SC QM.

Special Populations and Conditions

Population pharmacokinetic analyses based on data from 3414 patients suggest that age (18-80 years), race, or gender had no significant impact on REPATHA pharmacokinetics. Body weight influenced the pharmacokinetics of REPATHA without having notable impact on LDL-C reduction. Therefore, no dose adjustments are recommended based on these demographics.

Hepatic Impairment

Following a single 140 mg subcutaneous dose of REPATHA, the exposure to REPATHA was found to be approximately 40% to 50% lower in patients with mild or moderate hepatic impairment (N = 8) compared with healthy patients. However, the time course and extent of absolute LDL-C lowering effect were found to be similar between patients with mild or moderate hepatic impairment and healthy patients. Patients with severe hepatic impairment (Childs-Pugh C) have not been studied.

Renal Impairment

Population pharmacokinetic analysis of integrated data from the REPATHA clinical studies did not reveal a difference in pharmacokinetics between patients with no renal impairment and patients with mild or moderate renal impairment.

Single 140 mg subcutaneous doses of REPATHA were studied in 6 patients with normal renal function (estimated glomerular filtration rate [eGFR] $\geq$ 90 mL/min/1.73 m^2), 6 patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), and 6 patients with end stage renal disease (ESRD) receiving hemodialysis. The mean evolocumab exposure, as assessed by C_{max}, was found to be approximately 30% to 45% lower in patients with severe renal impairment and ESRD compared with patients with normal renal function. The pharmacodynamics of REPATHA in patients with severe renal impairment and ESRD were comparable to patients with normal renal function, and there were no clinically meaningful differences in LDL-C lowering.

STORAGE AND STABILITY

REPATHA prefilled syringes*, autoinjectors and automated mini-dosers with prefilled cartridges should be refrigerated at 2°C to 8°C in the original carton. If removed from the refrigerator, REPATHA should be kept at controlled room temperature up to 25°C in the original carton and must be used within 30 days.

Protect from direct light and temperatures above 25°C. Do not freeze. Do not shake. Do not use REPATHA beyond the expiration date.

SPECIAL HANDLING INSTRUCTIONS

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

The needle cover of the glass prefilled syringe* (PFS) and the autoinjector (AI) is made from dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex. There is no dry natural rubber in the automated mini-doser with prefilled cartridge.

* Prefilled syringes are not available in Canada

DOSAGE FORMS, COMPOSITION AND PACKAGING

REPATHA is provided as:

- One mL solution (140 mg/mL evolocumab) in a single use prefilled autoinjector with type 1 glass syringe and stainless steel needle (140 mg/mL AI); supplied as a 1-pack, 2-pack, and 3-pack.
- 3.5 mL solution in a single-use prefilled cartridge assembly made of Crystal Zenith® resin which is co-packaged with the administration device. The administration device is a compact, sterile, single-use, disposable, injection device intended for use only with the provided 3.5 mL prefilled cartridge assembly. (120 mg/mL AMD); supplied as a 1-pack.
- One mL solution (140 mg/mL evolocumab) in a single use prefilled syringe* made from type I glass with stainless steel needle (140 mg/mL PFS); supplied as a 1-pack.

REPATHA is a clear to opalescent, colourless to yellowish sterile, preservative-free solution, practically free from particles.

Each 1 mL prefilled syringe* and autoinjector contains 140 mg evolocumab, proline, glacial acetic acid, polysorbate 80, water for injection and sodium hydroxide.

Each 3.5 mL automated mini-doser and prefilled cartridge contains 420 mg evolocumab (120 mg/mL), proline, glacial acetic acid, polysorbate 80, water for injection and sodium hydroxide.

* Prefilled syringes are not available in Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Evolocumab
Chemical name:	anti-PCSK9 monoclonal antibody
Molecular weight:	144 kDa
Structural formula:	Evolocumab is a fully human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass consisting of 2 heavy chains and 2 light chains of the lambda subclass. Evolocumab contains 36 total cysteine residues involved in both intrachain and interchain disulfide bonds. Each heavy chain contains 441 amino acids with 4 intrachain disulfides. Each light chain contains 215 amino acids with 2 intrachain disulfides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 291.
Physicochemical properties:	Repatha® is a clear to opalescent, colourless to yellowish sterile, preservative-free solution, practically free from particles.

CLINICAL TRIALS

Prevention of Cardiovascular Events

Study Demographics and Trial Design

The cardiovascular outcomes study (FOURIER) was a phase 3, double-blind, randomized, placebo-controlled, event-driven, study to evaluate the effects of REPATHA treatment in adult patients with established cardiovascular disease as evidenced by a history of myocardial infarction, non-hemorrhagic stroke, or symptomatic peripheral arterial disease. Enrolled patients were required to have one or more additional major risk factors (e.g. diabetes mellitus, current daily cigarette smoking, age ≥ 65 years, or recent myocardial infarction [within 6 months]) or two or more minor risk factors (e.g. history of coronary revascularization, elevated non-HDL-C, metabolic syndrome). Eligible patients were required to be on a stable, moderate- to high-intensity statin background therapy at randomization consisting of an effective statin dose, i.e., at least atorvastatin 20 mg daily or equivalent, and where locally approved, highly effective statin therapy (defined as at least atorvastatin 40 mg daily or equivalent) was recommended. Patients with NYHA class III and class IV heart failure were excluded from the study.

A total of 27,564 (13,784 REPATHA; 13,780 placebo) adult patients were randomized 1:1 to receive either REPATHA (140 mg every 2 weeks or 420 mg once monthly) or placebo (every 2 weeks or once monthly, respectively) subcutaneously; 86% used the every 2 weeks regimen throughout the trial. Randomization was stratified by the final screening LDL-C level (< 2.2 mmol/L vs ≥ 2.2 mmol/L) and by geographical region (Europe, North America, Latin America and Asia Pacific).

The primary endpoint was the time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurred first. The key secondary endpoint was time to cardiovascular death, myocardial infarction, or stroke, whichever occurred first.

The study ended after a minimum of 1,630 patients had experienced a key secondary endpoint event of cardiovascular death, myocardial infarction, or stroke. Patients were to complete all planned visits regardless of their adherence to investigational product. 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% had 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 m^2 (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 2.4 (2.1, 2.8) mmol/L; the mean (SD) was 2.5 (0.7) mmol/L.

Study Results

REPATHA significantly reduced the risk for the primary composite endpoint (time to cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurred first) and the key secondary composite endpoint (time to cardiovascular death, myocardial infarction, or stroke, whichever occurred first). 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.

Table 3. Treatment Effects of REPATHA Compared with Placebo in Patients with Established Cardiovascular Disease (FOURIER)

	Placebo (N = 13780) n (%)	REPATHA (N = 13784) n (%)	Hazard Ratio (95% CI)	p-value [a]

	Placebo (N = 13780) n (%)	REPATHA (N = 13784) n (%)	Hazard Ratio (95% CI)	p-value [a]
Primary endpoint				
Time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurred first	1563 (11.34)	1344 (9.75)	0.85 (0.79, 0.92)	<0.0001
Key secondary endpoint				
Time to cardiovascular death, myocardial infarction, or stroke, whichever occurred first	1013 (7.35)	816 (5.92)	0.80 (0.73, 0.88)	<0.0001
Other secondary endpoints				
Time to cardiovascular death	240 (1.74)	251 (1.82)	1.05 (0.88, 1.25)	0.6188[b]
Time to death by any cause[c]	426 (3.09)	444 (3.22)	1.04 (0.91, 1.19)	
Time to first fatal or non-fatal myocardial infarction	639 (4.64)	468 (3.40)	0.73 (0.65, 0.82)	
Time to first fatal or non-fatal stroke	262 (1.90)	207 (1.50)	0.79 (0.66, 0.95)	
Time to first coronary revascularization	965 (7.00)	759 (5.51)	0.78 (0.71, 0.86)	
Time to first hospitalization for unstable angina[d]	239 (1.73)	236 (1.71)	0.99 (0.82, 1.18)	

[a] Two-sided log-rank test stratified by randomization stratification factors (final screening LDL-C and geographic region) collected via IVRS

[b] Based on pre-specified hierarchical nature of the statistical testing for multiplicity adjustment, the statistical testing could not be performed for the other secondary endpoints due to non-statistical significant result of time to cardiovascular death.

[c] Time to death by any cause is not a component of either the primary composite endpoint or key secondary composite endpoint

[d] 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. Cumulative Incidence Estimates for the Primary Composite Endpoint Over 3 Years

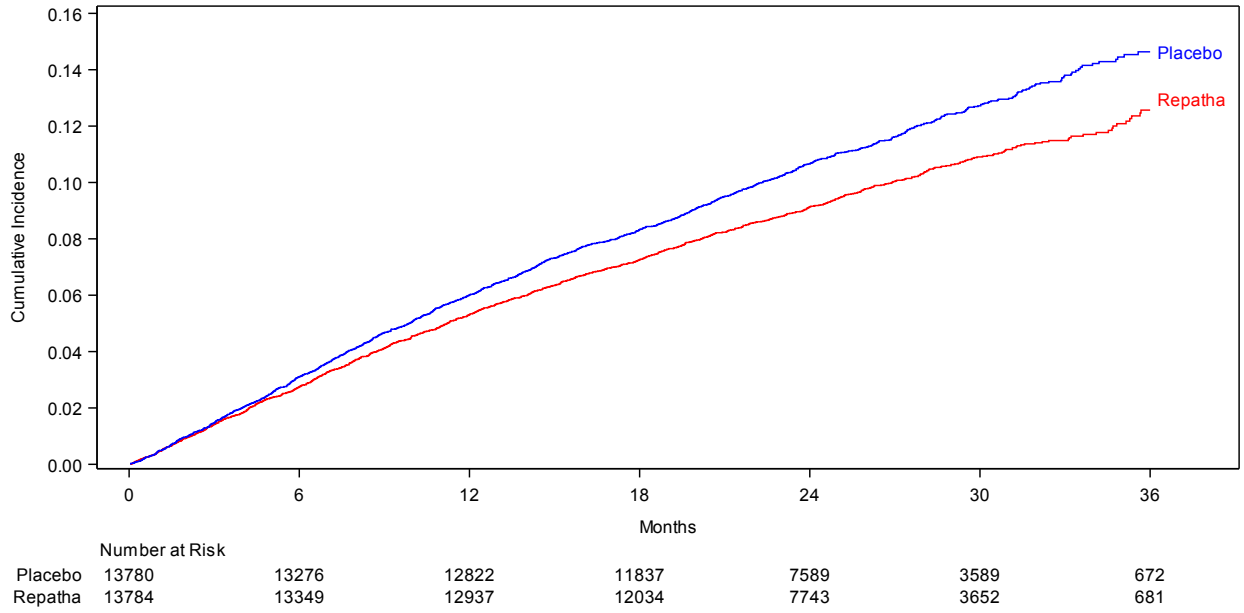
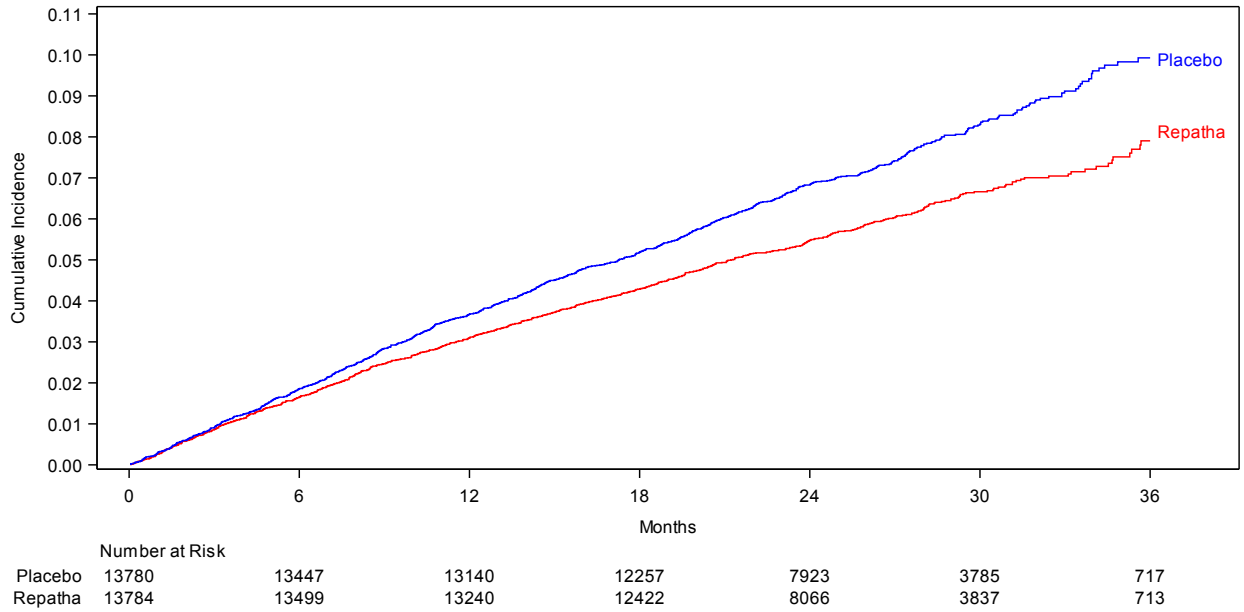


Figure 2. Cumulative Incidence Estimates for the Key Secondary Composite Endpoint Over 3 Years



The percent change from baseline at each scheduled assessment in LDL-C was assessed as an exploratory endpoint in the study. At Week 12, the LS (least squares) mean percent change from baseline in LDL-C was -2.42 in the placebo group and -63.11 in the REPATHA group. Of the patients treated with REPATHA, 9,518 (69.1%) achieved at least one LDL-C value < 0.65 mmol/L. The safety profile of REPATHA-treated patients with post-baseline LDL-C < 0.65 mmol/L was similar to that of REPATHA-treated patients with higher post-baseline LDL-C ≥ 1 mmol/L.

In a sub-study of 1,974 patients enrolled in the cardiovascular outcomes study, who had established cardiovascular disease, and who did not have mild cognitive impairment or dementia, REPATHA (n=586) was non-inferior to placebo (n=618) on select cognitive function domains assessed using neuropsychological function tests measured over a median follow-up of 19 months.

Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

Study Demographics and Trial Design

Table 4. Summary of Patient Demographics

Study #	Trial design	Dosage, Route of Administration and Duration	Study subjects (n)	Mean age (Range)	Gender
RUTHERFORD-2	Double-blind, randomized, placebo-controlled	REPATHA 140 mg SC Q2W REPATHA 420 mg SC QM Placebo SC Q2W Placebo SC QM	329	51.2 (19-79)	42.2% females

LAPLACE-2 Combination Therapy	Double-blind, randomized, placebo and ezetimibe-controlled, combination therapy	REPATHA 140 mg SC Q2W REPATHA 420 mg SC QM Placebo SC Q2W Placebo SC QM ezetimibe 10 mg PO QD	1,896	59.8 (20-80)	45.8% females
DESCARTES Long-Term Efficacy	Double-blind, Randomized, placebo-controlled, long term	REPATHA 420 mg SC QM Placebo SC QM	901	56.2 (25-75)	52.3% females
GAUSS-2 Statin-Intolerant	Double-blind, randomized, ezetimibe-controlled	REPATHA 140 mg SC Q2W REPATHA 420 mg SC QM Placebo PO QD Placebo SC Q2W Placebo SC QM Ezetimibe 10 mg PO QD	307	61.5 (22-80)	45.9% females

Q2W = once every 2 weeks; QM = once monthly; QD = once daily, SC = subcutaneously, PO = oral

RUTHERFORD-2 was an international, multicentre, double-blind, randomized, placebo-controlled, 12-week study of REPATHA in 329 patients with heterozygous familial hypercholesterolemia 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 this study 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 4.0 mmol/L with 76% of the patients on high- intensity statin therapy.

LAPLACE-2 was an international, multicentre, 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 1896 patients with primary hyperlipidemia (including 526 who had atherosclerotic cardiovascular disease) who received REPATHA or placebo as add-on therapy to daily doses of statins (atorvastatin 10 mg or 80 mg with or without ezetimibe 10 mg daily, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg). Among these patients, the mean age at baseline was 60 years (range: 20 to 80 years), 35% were ≥ 65 years old, 46% were women, 94% were White, 4% were Black, 1% were Asian and 5% were Hispanic or Latino. After 4 weeks background statin therapy, the mean baseline LDL-C was 2.8 mmol/L (range 2.3 – 3.2 mmol/L) across the five groups.

DESCARTES was an international, multicentre, double-blind, randomized, placebo-controlled, 52-week trial that included 901 patients with primary hyperlipidemia (including 156 who had atherosclerotic cardiovascular disease) who were assigned to background lipid lowering therapy based on underlying cardiovascular risk. Patients who did not reach target LDL-C goal on atorvastatin 80 mg also received ezetimibe 10 mg and thus had LDL-C levels more refractory to treatment. 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 56 years (range, 25 to 75 years), 23% were ≥ 65 years, 52% were women, 80% were White, 8% were Black, 6% were Asian, and 6% were

Hispanic or Latino. After stabilization on the assigned background therapy, the mean baseline LDL-C was 2.6 mmol/L (range 2.3 – 3.0 mmol/L) across the background therapy groups.

GAUSS-2 was a multicentre, double-blind, randomized, ezetimibe-controlled, 12-week trial that included 307 patients with primary hyperlipidemia (including 117 who had atherosclerotic cardiovascular disease) who had tried at least two different statins and who were unable to continue on the lowest effective dose of either due to intolerable myalgia, myositis or rhabdomyolysis (which resolved when the statins were discontinued or the doses reduced).. Patients were randomly assigned to receive subcutaneous injections of REPATHA 140 mg every 2 weeks, REPATHA 420 mg once monthly, or placebo every 2 weeks or monthly with ezetimibe 10 mg daily for 12 weeks. Among these patients, 55 patients were on statin therapy at baseline, while the mean age was 62 years (range: 22 to 80 years), 41% were ≥ 65 years old, 46% women, 94% White, 2% Black, 3% Asian, and 2.3% Hispanic or Latino. The mean baseline LDL-C was 5.0 mmol/L.

Study Results

In the RUTHERFORD-2 study, the differences between REPATHA and placebo group 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%, -53%; $p < 0.0001$) 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 RUTHERFORD-2)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Placebo every 2 weeks (n = 54)	-2	-1	-1	-2
REPATHA 140 mg every 2 weeks[†] (n = 110)	-63	-56	-50	-43
Mean difference from placebo	-61*	-55*	-49*	-41
(95% CI)	(-67, -55)	(-60, -49)	(-55, -44)	(-45, -36)
Placebo once monthly (n = 55)	4	5	5	3
REPATHA 420 mg once monthly[†] (n = 110)	-57	-50	-45	-37
Mean difference from placebo	-60*	-55*	-49*	-40
(95% CI)	(-68, -53)	(-62, -48)	(-56, -43)	(-46, -34)

[a] Calculated LDL-C.
Estimates are least squares means from a repeated measures model, which included treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.
Inferential statistics for total cholesterol are not presented since it was an exploratory endpoint.
* $p < 0.0001$ compared with placebo; type I error was controlled among all primary and secondary endpoints.
[†]140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

In the LAPLACE-2 study, the overall difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -73% (95% CI: -77%, -70%; $p < 0.0001$) and -64% (95% CI: -69%, -60%; $p < 0.0001$) 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: -51%, -40%; $p < 0.0001$) and -42% (95% CI: -48%, -37%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For individual results see Table 6.

Table 6. Effect of REPATHA on Lipid Parameters in Patients with Primary Hyperlipidemia on Atorvastatin 10 mg or 80 mg with or without Ezetimibe 10 mg daily, Rosuvastatin 5 mg or 40 mg, or Simvastatin 40 mg (Mean % Change from Baseline to Week 12 in LAPLACE-2)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Background Treatment with Atorvastatin 10 mg				
Q2W				
Placebo every 2 weeks (n = 56)	10	8	8	6
Ezetimibe 10 mg daily (n = 56)	-21	-18	-16	-14
REPATHA 140 mg every 2 weeks[†] (n = 110)	-65	-53	-51	-37
Mean difference of REPATHA from placebo (95% CI)	-74 * (-81, -68)	-62* (-67, -56)	-59* (-64, -54)	-43 (-47, -38)
Mean difference of REPATHA from Ezetimibe (95% CI)	-44** (-50, -37)	-35** (-41, -29)	-35** (-40, -30)	-23 (-27, -18)
QM				
Placebo once monthly (n = 55)	1	2	0	1
Ezetimibe 10 mg daily (n = 55)	-17	-15	-11	-11
REPATHA 420 mg once monthly[†] (n = 110)	-60	-53	-47	-37
Mean difference of REPATHA from placebo (95% CI)	-61* (-68, -54)	-55* (-61, -48)	-47* (-53, -42)	-38 (-43, -33)
Mean difference of REPATHA from Ezetimibe (95% CI)	-43** (-50, -36)	-38** (-44, -31)	-36** (-42, -30)	-25 (-30, -21)
Background Treatment with Atorvastatin 80 mg				
Q2W				
Placebo every 2 weeks (n = 55)	15	12	12	9
Ezetimibe 10 mg daily (n = 56)	-15	-14	-12	-10
REPATHA 140 mg every 2 weeks[†] (n = 109)	-65	-55	-50	-36
Mean difference of REPATHA from placebo (95% CI)	-80* (-91, -68)	-67* (-76, -57)	-61* (-69, -54)	-46 (-53, -39)
Mean difference of REPATHA from Ezetimibe (95% CI)	-50** (-61, -39)	-41** (-50, -31)	-37** (-45, -30)	-26 (-33, -20)
QM				
Placebo once monthly (n = 55)	12	10	7	6
Ezetimibe 10 mg daily (n = 54)	-21	-17	-12	-12
REPATHA 420 mg once monthly[†] (n = 110)	-62	-50	-46	-33
Mean difference of REPATHA from placebo (95% CI)	-74* (-84, -65)	-60* (-68, -52)	-53* (-61, -45)	-39 (-45, -33)
Mean difference of REPATHA from Ezetimibe (95% CI)	-41** (-51, -32)	-33** (-41, -24)	-34** (-42, -26)	-20 (-26, -14)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Background Treatment with Rosuvastatin 5 mg				
Q2W				
Placebo every 2 weeks (n = 58)	8	8	6	6
REPATHA 140 mg every 2 weeks† (n = 113)	-63	-52	-50	-36
Mean difference of REPATHA from placebo (95% CI)	-71* (-78, -64)	-60* (-66, -54)	-57* (-62, -51)	-43 (-47, -39)
QM				
Placebo once monthly (n = 57)	5	6	5	3
REPATHA 420 mg once monthly† (n = 115)	-61	-52	-49	-36
Mean difference of REPATHA from placebo (95% CI)	-66* (-72, -59)	-57* (-63, -52)	-53* (-58, -48)	-39 (-44, -35)
Background Treatment with Rosuvastatin 40 mg				
Q2W				
Placebo every 2 weeks (n = 56)	10	9	5	4
REPATHA 140 mg every 2 weeks† (n = 111)	-62	-51	-46	-33
Mean difference of REPATHA from placebo (95% CI)	-71* (-80,-63)	-60* (-67, -52)	-51* (-57, -44)	-38 (-42, -33)
QM				
Placebo once monthly (n = 55)	3	3	3	1
REPATHA 420 mg once monthly† (n = 112)	-56	-46	-44	-30
Mean difference of REPATHA from placebo (95% CI)	-59* (-69, -48)	-50* (-58, -41)	-47* (-54, -39)	-31 (-37, -25)
Background Treatment with Simvastatin 40 mg				
Q2W				
Placebo every 2 weeks (n = 56)	5	2	0	0
REPATHA 140 mg every 2 weeks† (n = 112)	-69	-59	-56	-42
Mean difference of REPATHA from placebo (95% CI)	-74* (-80, -67)	-61* (-67, -55)	-56* (-61, -51)	-42 (-47, -38)
QM				
Placebo once monthly (n = 55)	3	6	4	1
REPATHA 420 mg once monthly† (n = 115)	-59	-51	-49	-36
Mean difference of REPATHA from placebo (95% CI)	-62* (-71, -52)	-57* (-65, -49)	-53* (-59, -46)	-37 (-43, -31)

[a] Calculated LDL-C.

Estimates are least squares means from a repeated measures model, which included treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Inferential statistics for total cholesterol are not presented since it was an exploratory endpoint.

* $p < 0.0001$ compared with placebo; type I error was controlled among all primary and secondary endpoints.

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

**$p < 0.0001$ compared with ezetimibe; type I error was controlled among all primary and secondary endpoints.

In the DESCARTES study for these patients with primary hyperlipidemia on cholesterol-lowering diet alone, or on atorvastatin therapy with or without ezetimibe along with a cholesterol-lowering diet, the overall difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -59% (95% CI: -64%, -55%; $p < 0.0001$). For individual results see Table 7.

Table 7. Effect of REPATHA on Lipid Parameters in Patients with Primary Hyperlipidemia on Cholesterol-lowering Diet Alone, or Atorvastatin 10mg or 80 mg with or without Ezetimibe 10 mg daily along with a Cholesterol-lowering diet (Mean % Change from Baseline to Week 52 in DESCARTES)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Cholesterol-lowering Diet Alone				
Placebo once monthly (n = 37)	11	9	0	5
REPATHA 420 mg once monthly (n = 74)	-53	-45	-43	-31
Mean difference of REPATHA from placebo (95% CI)	-64* (-72, -55)	-54* (-62, -47)	-43* (-50, -36)	-36* (-42, -31)
Background Treatment with Atorvastatin 10 mg and Cholesterol-lowering Diet				
Placebo once monthly (n = 129)	8	9	3	5
REPATHA 420 mg once monthly (n = 254)	-56	-46	-45	-30
Mean difference of REPATHA from placebo (95% CI)	-64* (-70, -59)	-55* (-59, -50)	-48* (-52, -43)	-35* (-39, -32)
Background Treatment with Atorvastatin 80 mg and Cholesterol-lowering Diet				
Placebo once monthly (n = 73)	11	12	5	8
REPATHA 420 mg once monthly (n = 145)	-47	-38	-39	-25
Mean difference of REPATHA from placebo (95% CI)	-58* (-69, -46)	-50* (-60, -39)	-45* (-53, -36)	-33* (-40, -26)
Background Treatment with Atorvastatin 80 mg, Ezetimibe 10 mg and Cholesterol-lowering Diet				
Placebo once monthly (n = 63)	3	2	1	2
REPATHA 420 mg once monthly (n = 126)	-46	-39	-37	-27
Mean difference of REPATHA from placebo (95% CI)	-49* (-60, -38)	-41* (-51, -31)	-38* (-46, -29)	-29* (-36, -22)

[a] Calculated LDL-C.

Estimates are least squares means from a repeated measures model, which included treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.

* $p < 0.0001$ compared with placebo; type I error was controlled among all primary and secondary endpoints.

In the GAUSS-2 study, the difference between REPATHA and ezetimibe in mean percent change in LDL-C from baseline to Week 12 was -39% (95% CI: -45%, -34%; $p < 0.0001$) and -38% (95% CI: -43%, -33%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 8.

Table 8. Effect of REPATHA on Lipid Parameters in Patients with Primary Hyperlipidemia (Mean % Change from Baseline to Week 12 Compared to Ezetimibe in GAUSS-2)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Q2W				
Ezetimibe 10 mg daily (n = 51)	-18	-17	-13	-13
REPATHA 140 mg every 2 weeks[†] (n = 103)	-57	-49	-46	-38
Mean difference from Ezetimibe (95% CI)	-39** (-45, -34)	-32** (-37, -27)	-33** (-38, -28)	-25 (-29, -21)
QM				
Ezetimibe 10 mg daily (n = 51)	-15	-13	-10	-11
REPATHA 420 mg once monthly[†] (n = 102)	-53	-46	-43	-36
Mean difference from Ezetimibe (95% CI)	-38** (-43, -33)	-33** (-37, -29)	-33** (-38, -28)	-25 (-29, -22)

[a] Calculated LDL-C.
Estimates are least squares means from a repeated measures model, which included treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates.
Inferential statistics for total cholesterol are not presented since it was an exploratory endpoint.
[†]140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C
**$p < 0.0001$ compared with ezetimibe; type I error was controlled among all primary and secondary endpoints.

Homozygous Familial Hypercholesterolemia

Study Demographics and Trial Design

Table 9. Summary of Trial Design and Patient Demographics

Study #	Trial design	Dosage, Route of Administration and Duration	Study subjects (n)	Mean age (Range)	Gender
TESLA	Double-blind, randomized, placebo-controlled 12-week study	REPATHA 420 mg QM placebo SC QM	49	34.3 (13-57)	25% females
TAUSSIG	Ongoing, open-label long-term extension	REPATHA 420 mg QM REPATHA 420 mg Q2W	198	44.2 (13-77)	56.1% females

Q2W = once every 2 weeks; QM = once monthly; SC = subcutaneously.

TESLA Part B was a multicentre, double-blind, randomized, placebo-controlled, 12-week trial in 49 HoFH patients (not on lipid-apheresis therapy), 33 of whom received REPATHA 420 mg once monthly and 16 of whom received placebo, as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe, bile-acid sequestrants). The mean age at baseline was 31 years, 49% were female, 90% Caucasian, 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 9.0 mmol/L with all patients on statins 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 > 12.9 mmol/L together with either xanthoma before 10 years of age or evidence of HeFH in both parents. Twenty-four (49%) participants had homozygous genetic defects, 24 (49%) participants had compound heterozygous genetic defects and one had heterozygous genetic defects; overall, the gene affected was the LDLR for 96%. The primary endpoint was percent change from baseline in LDL-C at week 12.

TAUSSIG is an ongoing multicentre, open-label 5-year extension study to assess the long-term safety and efficacy of REPATHA in patients with severe familial hypercholesterolemia (FH), including homozygous familial hypercholesterolemia (HoFH), who were treated with REPATHA as an adjunct to other lipid lowering therapies. A total of 96 HoFH patients (65 non-apheresis and 31 apheresis) enrolled in TAUSSIG. All patients in the study were initially treated with REPATHA 420 mg once monthly except for those receiving apheresis at enrollment, who began with REPATHA 420 mg every two weeks. Dose frequency in non-apheresis patients could be titrated up to 420 mg once every 2 weeks based on LDL-C response and PCSK9 levels. Of the 65 non-apheresis HoFH patients in TAUSSIG (who started on the 420 mg QM dose), 30 patients up-titrated to the 420 mg Q2W dose, with 25 of these 30 patients having received ≥ 12 weeks of both doses. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 13.0 mmol/L together with either xanthoma before 10 years of age or evidence of HeFH in both parents. The statistical analysis of efficacy data from this study is descriptive in nature, and no hypotheses were tested.

Homozygous Familial Hypercholesterolemia

In Part B of TESLA, REPATHA 420 mg once monthly significantly reduced LDL-C at week 12 as compared with placebo: mean percent change from baseline to Week 12 was -32% (95% CI: -45%, -19%; p<0.001). For additional information see Table 10.

Table 10. Effect of REPATHA on Lipid Parameters in Patients with Homozygous Familial Hypercholesterolemia (Mean % Change from Baseline to Week 12 in TESLA)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 16)	9	8	4	8
REPATHA 420 mg once monthly (n = 33)	-23	-22	-19	-19
Mean difference of REPATHA from placebo (95% CI)	-32* (-45,-19)	-30 (-42, -18)	-23* (-35,-11)	-27 (-38, -16)

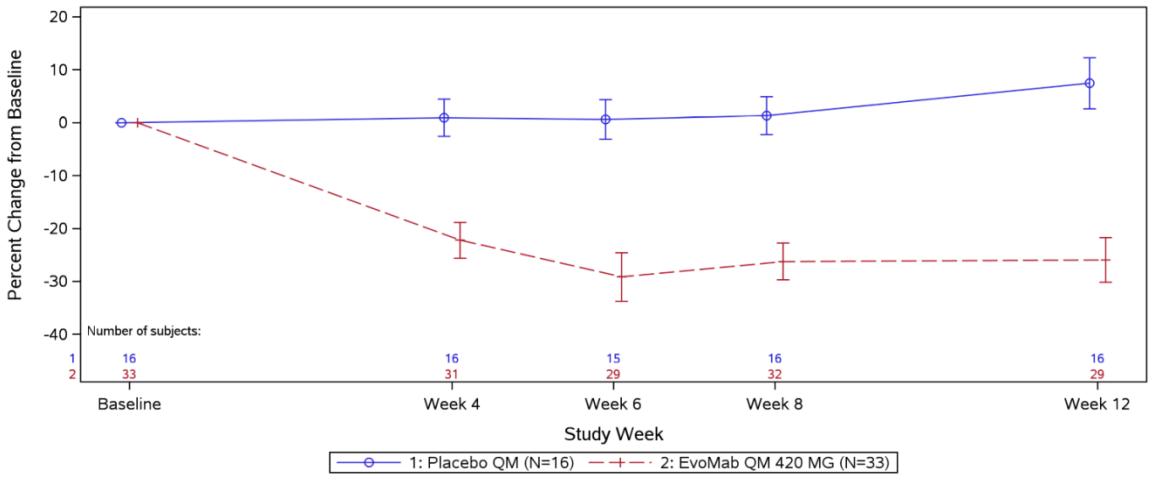
[a] Calculated LDL-C.

Estimates are least squares means from a repeated measures model, which included treatment group, screening LDL-C, scheduled visit and the interaction of treatment with scheduled visit as covariates.

Inferential statistics for non-HDL-C and total cholesterol are not presented since it was an exploratory endpoint.

* p < 0.001 compared with placebo; type I error was controlled among all primary and secondary endpoints.

Figure 3. Effect of REPATHA on LDL-C in Patients with HoFH – Mean Percent Change from Baseline by Scheduled Visit and Treatment Group



N = number of patients that were randomized and dosed in the full analysis set; EvoMab = Evolocumab; QM = monthly.
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

Long-term Study in Patients with HoFH

Based on interim study results (TAUSSIG), long-term use of REPATHA demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with HoFH (overall, non-apheresis and apheresis) (Table 11). Changes in other lipid parameters (total cholesterol, ApoB, and non-HDL-C,) also demonstrate a sustained effect of long-term REPATHA administration in patients with HoFH.

Table 11. Effect of REPATHA on LDL-C in Patients with HoFH (Mean % Change from Baseline to OLE Week 36 in TAUSSIG)

Patient Population (N)	OLE Week 12	OLE Week 24	OLE Week 36
HoFH (N = 96)	-20 (n = 70)	-23 (n = 46)	-24 (n = 30)
Median	-16	-21	-23
Range	-92, 38	-74, 46	-69, 28
Non-apheresis (N = 65)	-22 (n = 46)	-24 (n = 33)	-24 (n = 27)
Median	-20	-21	-26
Range	-85, 23	-74, 34	-69, 28
Apheresis (N = 31)	-17 (n = 24)	-20 (n = 13)	-21 (n = 3)
Median	-15	-23	-10
Range	-92, 38	-58, 46	-67, 12

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

A total of 25 patients were included in the HoFH Evolocumab Titration Analysis Set, which included non-apheresis patients who received evolocumab 420 mg QM for at least 12 weeks in the OLE study followed by evolocumab 420 mg Q2W for at least 12 weeks in the OLE study. Mean percent reductions from baseline in LDL-C were 15% at week 12 of QM treatment and 21% at week 12 of Q2W treatment.

Among 13 adolescent patients with HoFH, mean percent reduction from baseline in LDL-C at OLE week 12 was 13%.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

The in vivo effects of evolocumab were evaluated in the hamster and cynomolgus monkey. Administration of evolocumab caused up-regulation of hepatic LDLR protein levels in the hamster model; effects on hepatic LDLR protein were not evaluated in the cynomolgus monkey model. The administration of evolocumab significantly reduced the levels of serum LDL-C in hamsters and cynomolgus monkeys.

In the hamster model, in vivo administration of evolocumab also reduced the levels of serum high-density lipoprotein cholesterol (HDL-C). Unlike in humans, HDL particles are ligands for the LDLR in hamsters.

In the cynomolgus monkey model, the effects on serum lipoproteins of evolocumab administration were studied over a wide range of SC single doses (0.05, 0.2, 0.5, 3, 10, 30 mg/kg). Evolocumab caused a mean reduction in LDL-C in all of the dose groups that was statistically significant ($p < 0.01$) except for the 0.05 mg/kg group. LDL-C subsequently returned to baseline levels with the time of return (i.e., duration of effect) being dose-dependent.

Evolocumab administration was not associated with changes in HDL-C or triglycerides in monkeys. Decreases in serum PCSK9 were immediate and resulted in serum unbound PCSK9 concentrations below the level of quantitation within one day of dose administration. The reduction of unbound PCSK9 preceded the nadir of mean reduction in LDL-C (approximately 80% at 1 week post-dose administration). The return of PCSK9 concentrations toward baseline was paralleled by the return of LDL-C toward baseline.

Pharmacokinetics

The key evolocumab PK and toxicokinetic (TK) characteristics determined in hamster and cynomolgus monkey indicated:

- nonlinear PK, dose-dependent changes in both unbound apparent clearance (CL/F) and volume of distribution (V_{ss}/F) and changes in unbound target (PCSK9)
- an estimated SC absolute bioavailability of 82%
- low volumes of distribution typical of monoclonal antibodies likely indicating limited distribution in tissue
- a low prevalence of anti-evolocumab antibody development

- the relationship between unbound evolocumab and LDL-C serum concentrations was well described by a semi-mechanistic PKPD model
- no evidence of gender differences, unanticipated accumulation or time dependent changes in evolocumab TK following multiple dose administration.

TOXICOLOGY

No adverse effects were observed in hamsters and cynomolgus monkeys administered REPATHA at dose levels up to 300 mg/kg bw QW for 3 and 6 months, respectively. The intended pharmacological effect of decreased serum LDL-C and total cholesterol was observed in these studies and was reversible upon cessation of treatment.

No adverse effects were observed when REPATHA was administered in combination with rosuvastatin to cynomolgus monkeys at dose levels of 100 mg/kg bw QM and 5mg/kg bw QD, respectively, for 3 months. Reductions in serum LDL-C and total cholesterol were more pronounced than observed previously with REPATHA alone, and were reversible upon cessation of treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a life time pharmacology study, REPATHA was not carcinogenic in hamsters administered dose levels of 100 mg/kg bw Q2W. Genotoxicity and mutagenicity studies were not conducted. Fertility endpoints (including estrous cycling, sperm analysis, mating performance and embryonic development) were not affected in hamsters administered dose levels of 50 mg/kg bw Q2W for 3 months. In sexually mature cynomolgus monkeys, no effects were observed on reproductive organ weight or histopathology, menstrual cycling or sperm parameters following administration of REPATHA at dose levels up to 300 mg/kg bw QW for 6 months.

Embryo-fetal and post-natal development (including skeletal, neurobehavioural and external/ visceral assessments) were not affected in offspring of pregnant cynomolgus monkeys administered 50 mg/kg bw Q2W from gestational day (GD) 20-22 until parturition. Treated mothers displayed up to a 70% reduction in serum LDL-C compared to control females. Offspring of REPATHA treated mothers were exposed to therapeutic levels of REPATHA via placental transfer and displayed no reductions in serum LDL-C.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{Pr}REPATHA®
(evolocumab)

Single-use Prefilled SureClick® Autoinjector

Read this carefully before you start taking REPATHA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REPATHA. Keep this leaflet, as you may need to read it again.

What is REPATHA used for?

REPATHA is used:

- along with diet and in combination with usual therapy, including cholesterol-lowering medications called statins, to reduce the risk of heart attack, stroke, and certain heart procedures (to restore blood flow to the heart) in adult patients who have cardiovascular disease.
- alone or together with other cholesterol-lowering medicines, along with diet, in adults with primary hyperlipidemia (high cholesterol level in your blood) to reduce LDL cholesterol.
- along with diet and other LDL lowering therapies in people with homozygous familial hypercholesterolemia 12 years and older (an inherited condition that causes high levels of LDL), who need additional lowering of LDL cholesterol.

It is not known if REPATHA is safe and effective in children with homozygous familial hypercholesterolemia (HoFH) who are younger than 12 years of age or in children with primary hyperlipidemia who are younger than 18 years of age.

How does REPATHA work?

REPATHA is a medicine used to lower levels of cholesterol. REPATHA lowers levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, REPATHA raises levels of "good" cholesterol (HDL cholesterol).

Evolocumab, the active ingredient of REPATHA, works by helping the liver's ability to remove bad cholesterol from the blood. Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol. LDL cholesterol is often called "bad" cholesterol because it can build up in the walls of your arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke and can cause other health problems. HDL cholesterol is often called "good" cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease. Triglycerides are another form of fat in your blood that may increase your risk of heart disease.

What are the ingredients in REPATHA?

The active substance is evolocumab.

- Each 1 mL prefilled autoinjector contains 140 mg of evolocumab (140 mg/mL)
- Each 3.5 mL prefilled cartridge contains 420 mg of evolocumab (120 mg/mL)
- Each 1 mL prefilled syringe* contains 140 mg of evolocumab (140 mg/mL)

The other ingredients are proline, glacial acetic acid, polysorbate 80, water for injection, sodium hydroxide.

REPATHA comes in the following dosage forms:

REPATHA is available in the presentations listed below. Your doctor will prescribe the type that is best for you.

- 140 mg/mL 1 mL single-use prefilled autoinjector (SureClick®)
- 120 mg/mL 3.5 mL prefilled cartridge with an automated mini-doser (AMD)
- 140 mg/mL 1 mL single-use prefilled syringe*

Do not use REPATHA if:

You should not take REPATHA if you have ever had an allergic reaction to REPATHA or any of the ingredients in REPATHA.

To help avoid effects and ensure proper use, talk to your healthcare professional before you take REPATHA. Talk about any health conditions or problems you may have.

If you use REPATHA together with a statin and other cholesterol lowering medicines, please read the package leaflet of that particular medicine.

If you have allergies, or 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. There is no dry natural rubber in the automated mini-doser with prefilled cartridge.

Children and adolescents

The use of REPATHA has not been studied in children under 18 years of age being treated for primary hyperlipidemia. The use of REPATHA has not been studied in children under 12 years of age being treated for homozygous familial hypercholesterolemia.

Other Medicines and REPATHA

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

*Prefilled syringes are not available in Canada

Pregnancy and Breastfeeding

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

If you are trying to get pregnant or think you may be pregnant when taking REPATHA:

- Inform your doctor
- If you are also taking a statin along with REPATHA, stop taking REPATHA and read the package leaflet of the statin that you are taking with REPATHA

If you become pregnant while taking REPATHA, talk to your healthcare provider about registering in the pregnancy exposure registry for REPATHA. You can enroll in this registry by calling 1-877-311-8972 or by visiting https://mothertobaby.org/ongoing-study/repatha/. The purpose of this registry is to collect information about the safety of REPATHA during pregnancy.

It is not known whether REPATHA is found in breast milk. It is important to tell your doctor if you are breastfeeding or plan to do so. Your doctor will then help you decide whether to stop breastfeeding, or whether to stop taking REPATHA, considering the benefit of breastfeeding to the baby and the benefit of REPATHA to the mother.

How to take REPATHA:

REPATHA is given as an injection under the skin (subcutaneous or SC). REPATHA is available in the presentations listed below. Your doctor will prescribe the type that is best for you.

- Single-use prefilled autoinjector (SureClick®)
- Single-use automated mini-doser
- Single-use prefilled syringe*

If your doctor decides that you or a caregiver can give the injections of 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.

- When using the prefilled autoinjector (SureClick®), place the correct (yellow) end of the autoinjector on the skin before injecting (Please see the detailed Instructions for Use below).

Always take REPATHA exactly as your doctor has told you. Check with your doctor if you are not sure.

- Before starting REPATHA, you should be on a diet to lower your cholesterol.
- You should stay on this cholesterol lowering diet while taking REPATHA.

If your doctor has prescribed REPATHA along with a statin or other cholesterol lowering medicine, follow your doctor's instructions on how to take these medicines together. In this case, please read the dosage instructions in the package leaflet of the other medicines.

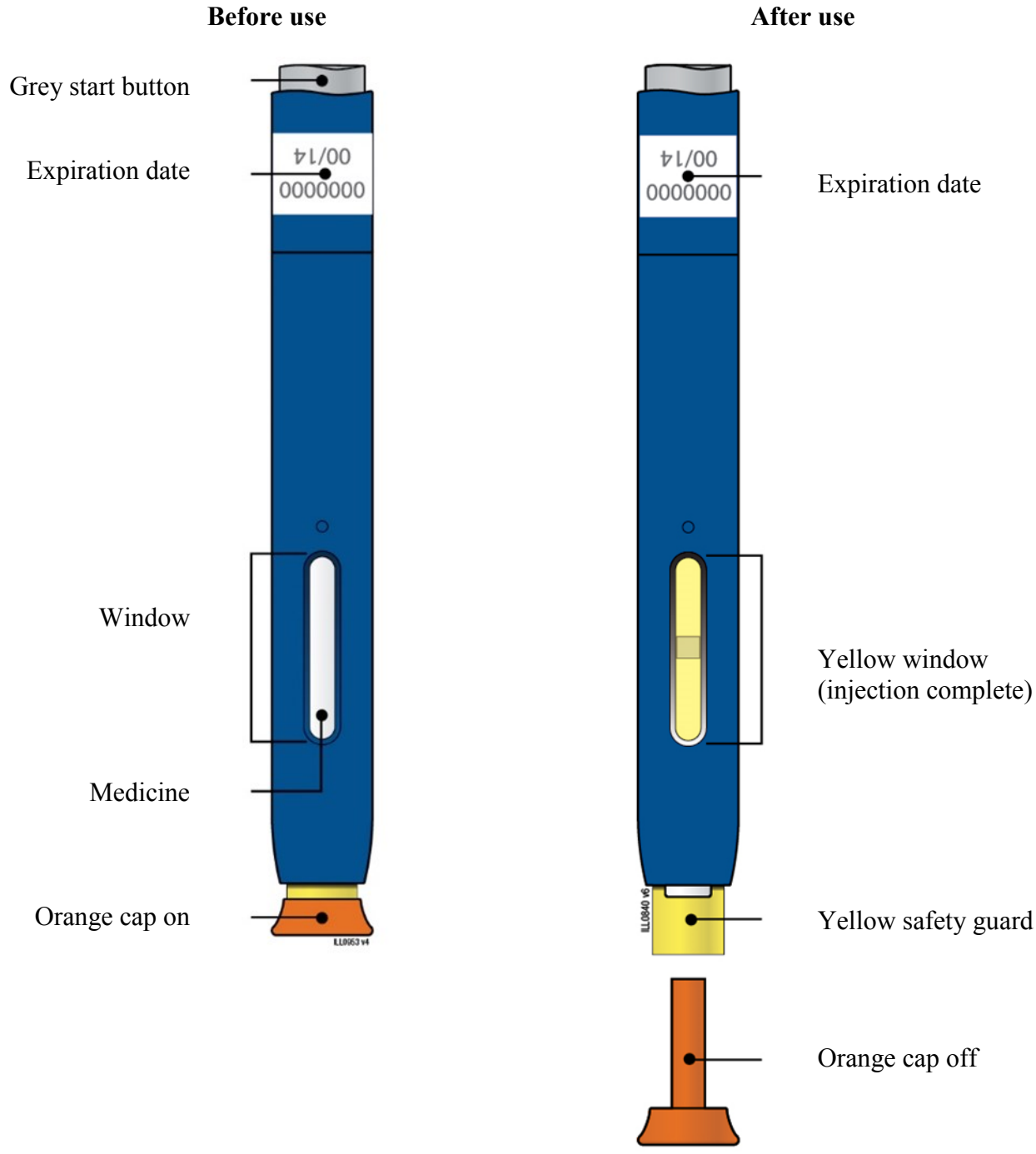
Ask your doctor if you have any further questions on how to use REPATHA.

*Prefilled syringes are not available in Canada

REPATHA Single-Use Prefilled SureClick® Autoinjector

The following instructions are for preparing and giving an injection of REPATHA using a single-use prefilled SureClick® autoinjector.

Guide to Parts



Important: Needle is inside

Important

Before you use the REPATHA SureClick® autoinjector, read this important information:

- Keep the REPATHA SureClick® autoinjector in original carton to protect from light during storage.
- The REPATHA SureClick® autoinjector should be kept in the refrigerator (2°C to 8°C).
- It is important that you do not try to give yourself the injection unless you have received training from your healthcare provider.
- The orange cap on a REPATHA SureClick® autoinjector contains a needle cover (located inside the cap) that is composed of dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.
- Keep the REPATHA SureClick® autoinjector out of sight and reach of children.
- **Do not** freeze or use the REPATHA SureClick® autoinjector if it has been frozen.
- **Do not** shake the REPATHA SureClick® autoinjector.
- **Do not** remove the orange cap from the REPATHA SureClick® autoinjector until you are ready to inject.
- **Do not** use the REPATHA SureClick® autoinjector if it has been dropped on a hard surface. Part of the REPATHA SureClick® autoinjector may be broken even if you cannot see the break. Use a new REPATHA SureClick® autoinjector.
- **Do not** use the REPATHA SureClick® autoinjector after the expiration date.

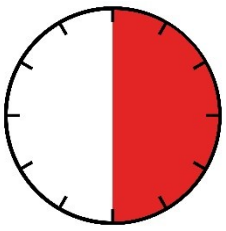
A healthcare provider familiar with REPATHA should be able to answer your questions. For more information, contact the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

Step 1: Prepare

A. Remove one REPATHA SureClick® autoinjector from the package.

1. Carefully lift the autoinjector straight up out of the box.
2. Put the original package with any unused autoinjectors back in the refrigerator.
3. Wait at least 30 minutes for the autoinjector to naturally reach room temperature before injecting.

   - **Do not** try to warm the autoinjector by using a heat source such as hot water or microwave.
   - **Do not** leave the autoinjector in direct sunlight.
   - **Do not** shake the autoinjector.
   - **Do not** remove the orange cap from the autoinjector yet.



30 minutes

B. Inspect the REPATHA SureClick® autoinjector.

Orange cap on | Window | Medicine

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

Check the expiration date.

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

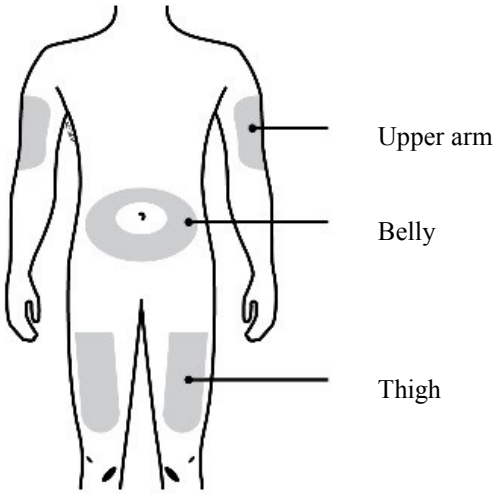
In all cases, use a new autoinjector, and contact the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842).

C. Gather all materials needed for your injection.

Wash your hands thoroughly with soap and water. **On a clean, well-lit work surface, place the:**

- New autoinjector
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container

D. Prepare and clean your injection site.



You can use:

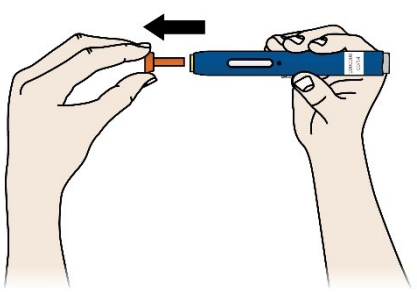
- Thigh
- Belly, except for a **five** centimeter (two inch) area around your belly button
- Outer area of upper arm (only if someone else is giving you the injection)

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

- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection. If you need to use the same injection site, just make sure it is not the same spot on that site you used last time.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

Step 2: Get ready

A. Pull the orange cap straight off, only when you are ready to inject. **Do not** leave the orange cap off for more than five minutes. This can dry out the medicine and may clog the needle when you take the injection.



5 minutes

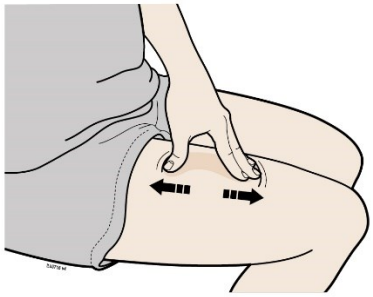
It is normal to see a drop of liquid at the end of the needle or yellow safety guard.

- **Do not** twist, bend or wiggle the orange cap
- **Do not** put the orange cap back onto the autoinjector
- **Do not** put fingers into the yellow safety guard

Important: Do not remove the orange cap from the autoinjector until you are ready to inject. If you are unable to inject, please contact your healthcare provider.

B. Stretch or pinch your injection site to create a firm surface.

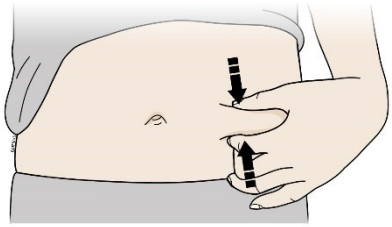
Stretch Method



Stretch skin firmly by moving your thumb and fingers in opposite directions, creating an area about five centimeters (two inches) wide.

OR

Pinch method

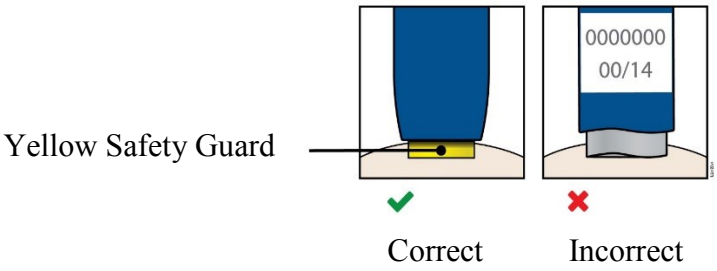


Pinch skin firmly between your thumb and fingers, creating an area about five centimeters (two inches) wide.

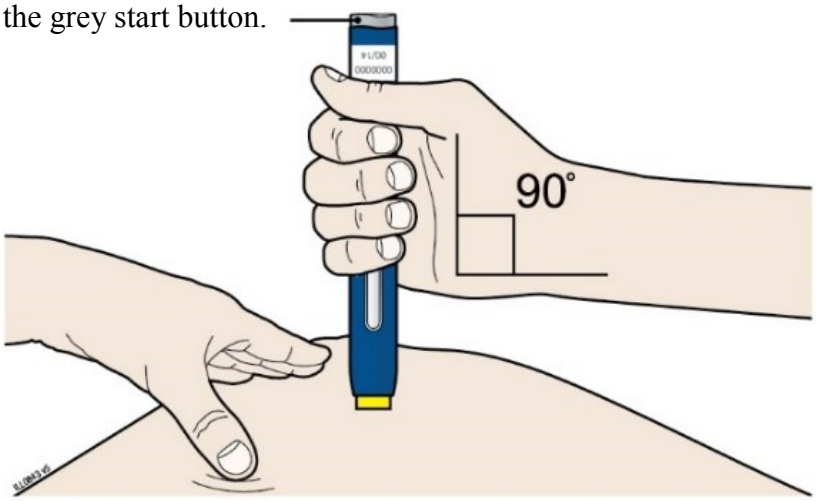
Important: It is important to keep skin stretched or pinched while injecting.

Step 3: Inject

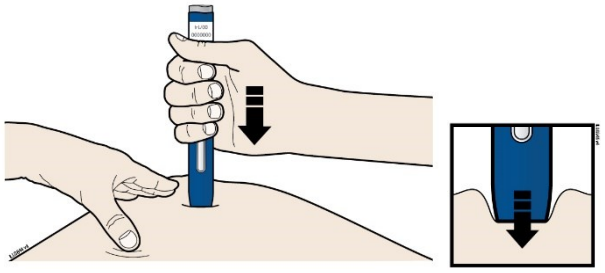
A. Hold the stretch or pinch to create a firm surface. With the cap off, **place** the yellow end of the autoinjector on the skin at 90 degrees.



Do not touch the grey start button.



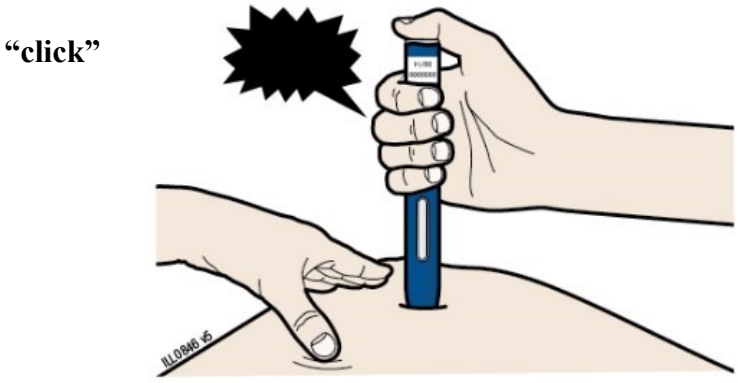
B. Firmly **push** down autoinjector onto skin until it stops moving.



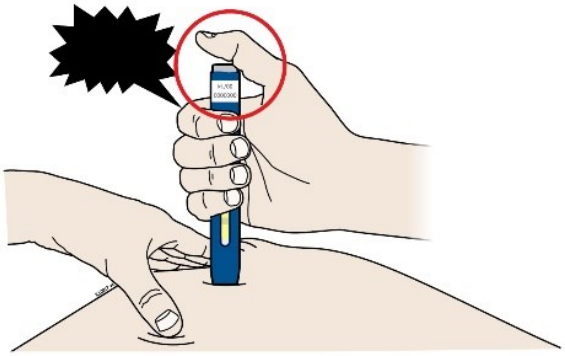
Push down

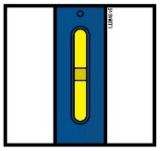
Important: You must push all the way down but **do not** touch the grey start button until you are ready to inject.

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

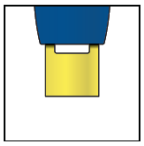


D. Keep **pushing** down on skin. Then **lift** thumb. Your injection could take about 15 seconds.





Window turns yellow when the injection is done



NOTE: After you remove the autoinjector from your skin, the needle will be automatically covered.

Step 4: Finish

A. Discard the used autoinjector and orange needle cap.

Discard the used autoinjector and the orange cap in a sharps disposal container.

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

Keep the autoinjector and the sharps disposal container out of the sight and reach of children.

- **Do not** reuse the autoinjector
- **Do not** recap the autoinjector or put fingers into the yellow safety guard
- **Do not** recycle the autoinjector or sharps disposal container or throw them into household trash

B. Examine the injection site.

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

Commonly Asked Questions:

What will happen if I press the grey start button before I am ready to do the injection on my skin?

You can lift your finger up off the grey start button and place the prefilled autoinjector back on your injection site. Then, you can push the grey start button again.

Can I move the autoinjector around on my skin while I am choosing an injection site?

It is okay to move the autoinjector around on the injection site as long as you do not press the grey start button. However, if you press the grey start button and the yellow safety guard is pushed into the autoinjector, the injection will begin.

Can I release the grey start button after I start my injection?

You can release the grey start button, but continue to hold the autoinjector firmly against your skin during the injection.

Will the grey start button pop up after I release my thumb?

The grey start button may not pop up after you release your thumb if you held your thumb down during the injection. This is okay.

What do I do if I did not hear a second click?

If you did not hear a second click, you can confirm a complete injection by checking that the window has turned yellow.

Whom do I contact if I need help with the autoinjector or my injection?

A healthcare provider familiar with REPATHA should be able to answer your questions. For more information, contact the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

Usual Dose:

Prevention of Cardiovascular Events and Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The usual dose for REPATHA is 140 mg every 2 weeks or 420 mg once monthly. If you and your doctor have decided that you should switch from one dosing regimen to the other, take the first dose of the new regimen on the day you were scheduled to take the previous one.

Homozygous Familial Hypercholesterolemia

The usual dose for REPATHA is 420 mg, either once monthly or every 2 weeks. If you are on apheresis you may initiate treatment with 420 mg every 2 weeks to correspond with your apheresis schedule.

Overdose:

If you think you have taken too much REPATHA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your every 2 week or once monthly dose of REPATHA or are not able to take the dose at the regular time, administer your missed dose as soon as you remember, as long as there are more than 7 days until your next scheduled dose. If there are 7 days or less until your next scheduled dose, administer the next dose according to the original schedule. This will put you back on your original schedule. If you are not sure when to take REPATHA after a missed dose, ask your healthcare provider or pharmacist.

What are possible side effects from using REPATHA:

Like all medicines, REPATHA can cause side effects, although not everybody gets them. REPATHA may cause allergic reactions. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction including a severe rash, redness, severe itching, a swollen face or trouble breathing. The following are possible side effects when taking REPATHA. If you experience any side effects not listed here, or if any side effect becomes bad enough to interfere with your daily activities, contact your healthcare professional.

- Flu or flu-like symptoms (high temperature, sore throat, runny nose, cough and chills)
- Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections)
- Nausea
- Back pain
- Joint pain (arthralgia)
- High blood sugar levels (diabetes)

- Injection site reactions (redness, bruising, pain, swelling, or bleeding)
- Allergic reactions including rash, hives, red itchy bumps on your skin (urticaria), and in rare cases, swelling of face, mouth, tongue or throat (angioedema)

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect®;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect® http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store in a refrigerator at 2°C to 8°C in the original carton. When removed from the refrigerator, REPATHA should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days. Protect REPATHA from direct light and do not expose to temperatures above 25°C. Do not freeze. Do not shake.

Keep REPATHA and all medicines out of the reach from children.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use.

If you want more information about REPATHA:

Talk to your healthcare professional.

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842) or by visiting www.repatha.ca.

This leaflet was prepared by Amgen Canada Inc.

Last Revised: February 27, 2019

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrREPATHA®
(evolocumab)

Single-use Prefilled Cartridge with Automated Mini-Doser (AMD)

Read this carefully before you start taking REPATHA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REPATHA. Keep this leaflet, as you may need to read it again.

What is REPATHA used for?

REPATHA is used:

- along with diet and in combination with usual therapy, including cholesterol-lowering medications called statins, to reduce the risk of heart attack, stroke, and certain heart procedures (to restore blood flow to the heart) in adult patients who have cardiovascular disease.
- alone or together with other cholesterol-lowering therapies, along with diet, in adults with primary hyperlipidemia (high cholesterol level in your blood) to reduce LDL cholesterol.
- along with diet and other LDL lowering therapies in people with homozygous familial hypercholesterolemia 12 years and older (an inherited condition that causes high levels of LDL), who need additional lowering of LDL cholesterol.

It is not known if REPATHA is safe and effective in children with homozygous familial hypercholesterolemia (HoFH) who are younger than 12 years of age or in children with primary hyperlipidemia who are younger than 18 years of age.

How does REPATHA work?

REPATHA is a medicine used to lower levels of cholesterol. REPATHA lowers levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, REPATHA raises levels of "good" cholesterol (HDL cholesterol).

Evolocumab, the active ingredient of REPATHA, works by helping the liver's ability to remove bad cholesterol from the blood. Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol. LDL cholesterol is often called "bad" cholesterol because it can build up in the walls of your arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke and can cause other health problems. HDL cholesterol is often called "good" cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease. Triglycerides are another form of fat in your blood that may increase your risk of heart disease.

What are the ingredients in REPATHA?

The active substance is evolocumab.

- Each 1 mL prefilled autoinjector contains 140 mg of evolocumab (140 mg/mL)
- Each 3.5 mL prefilled cartridge contains 420 mg of evolocumab (120 mg/mL)
- Each 1 mL prefilled syringe* contains 140 mg of evolocumab (140 mg/mL)

The other ingredients are proline, glacial acetic acid, polysorbate 80, water for injection, sodium hydroxide.

REPATHA comes in the following dosage forms:

REPATHA is available in the presentations listed below. Your doctor will prescribe the type that is best for you.

- 140 mg/mL 1 mL single-use prefilled autoinjector (SureClick®)
- 120 mg/mL 3.5 mL prefilled cartridge with an automated mini-doser (AMD)
- 140 mg/mL 1 mL single-use prefilled syringe*

Do not use REPATHA if:

You should not take REPATHA if you have ever had an allergic reaction to REPATHA or any of the ingredients in REPATHA.

To help avoid effects and ensure proper use, talk to your healthcare professional before you take REPATHA. Talk about any health conditions or problems you may have.

If you use REPATHA together with a statin and other cholesterol lowering medicines, please read the package leaflet of that particular medicine.

If you have allergies, or 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. There is no dry natural rubber in the automated mini-doser with prefilled cartridge.

Children and adolescents

The use of REPATHA has not been studied in children under 18 years of age being treated for primary hyperlipidemia. The use of REPATHA has not been studied in children under 12 years of age being treated for homozygous familial hypercholesterolemia.

Other Medicines and REPATHA

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

*Prefilled syringes are not available in Canada

Pregnancy and Breastfeeding

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

If you are trying to get pregnant or think you may be pregnant when taking REPATHA:

- Inform your doctor
- If you are also taking a statin along with REPATHA, stop taking REPATHA and read the package leaflet of the statin that you are taking with REPATHA

If you become pregnant while taking REPATHA, talk to your healthcare provider about registering in the pregnancy exposure registry for REPATHA. You can enroll in this registry by calling 1-877-311-8972 or by visiting https://mothertobaby.org/ongoing-study/repatha/. The purpose of this registry is to collect information about the safety of REPATHA during pregnancy.

It is not known whether REPATHA is found in breast milk. It is important to tell your doctor if you are breastfeeding or plan to do so. Your doctor will then help you decide whether to stop breastfeeding, or whether to stop taking REPATHA, considering the benefit of breastfeeding to the baby and the benefit of REPATHA to the mother.

How to take REPATHA:

REPATHA is given as an injection under the skin (subcutaneous or SC). REPATHA is available in the presentations listed below. Your doctor will prescribe the type that is best for you.

- Single-use prefilled autoinjector (SureClick®)
- Single-use automated mini-doser
- Single-use prefilled syringe*

If your doctor decides that you or a caregiver can give the injections of 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.

Always take REPATHA exactly as your doctor has told you. Check with your doctor if you are not sure.

- Before starting REPATHA, you should be on a diet to lower your cholesterol.
- You should stay on this cholesterol lowering diet while taking REPATHA.

If your doctor has prescribed REPATHA along with a statin or other cholesterol lowering medicine, follow your doctor's instructions on how to take these medicines together. In this case, please read the dosage instructions in the package leaflet of the other medicines.

Ask your doctor if you have any further questions on how to use REPATHA.

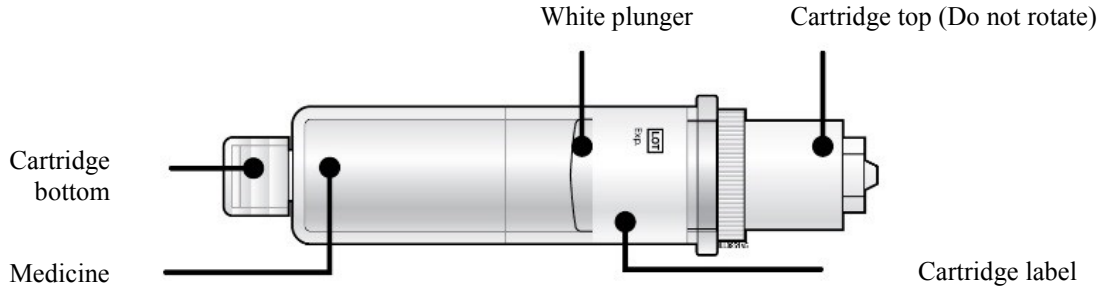
*Prefilled syringes are not available in Canada

REPATHA Automated Mini-Doser and Prefilled Cartridge

The following instructions are for preparing and giving an injection of REPATHA using an automated mini-doser and single-use prefilled cartridge.

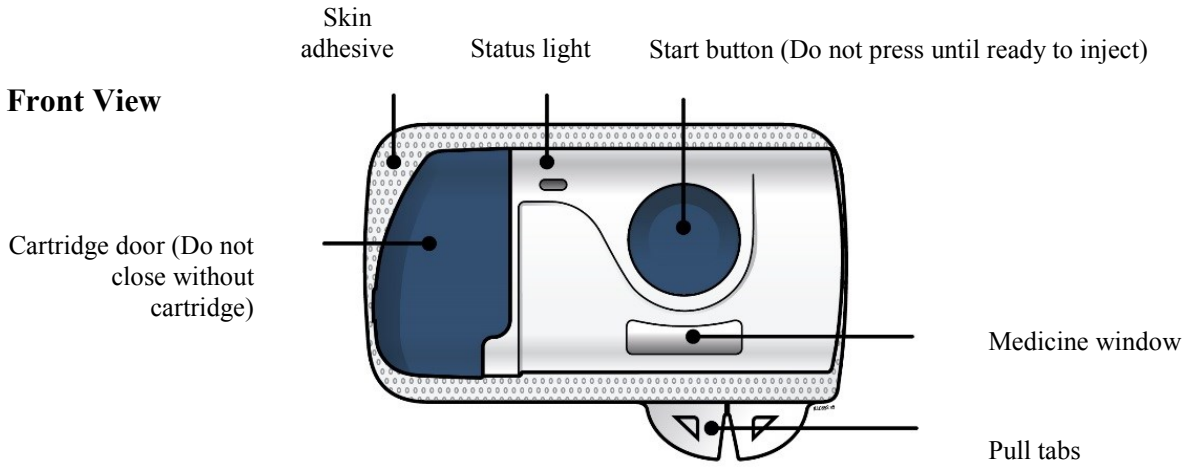
Guide to Parts

Prefilled Cartridge

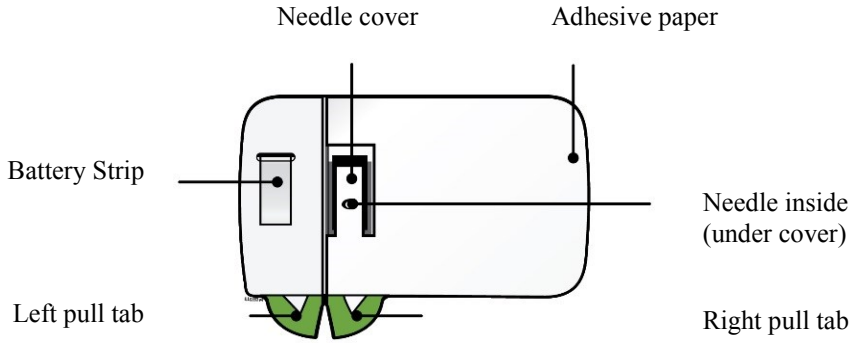


Automated Mini-Doser

Front View



Back View



Important: Needle is inside.

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

Storing your automated mini-doser and prefilled cartridge

- Keep the automated mini-doser and prefilled cartridge out of the reach of children.
- Keep the automated mini-doser and prefilled cartridge in the original carton to protect from light or physical damage.
- The automated mini-doser and prefilled cartridge must be kept in the refrigerator at 2ºC to 8ºC.
- If removed from the refrigerator, the automated mini-doser and prefilled cartridge should be kept at room temperature at 20°C to 25°C in the original carton and must be used within 30 days.
- **Do not** store the automated mini-doser and prefilled cartridge in extreme heat (e.g., Above 25ºC) or cold (e.g., avoid storing in your vehicle's glove box or trunk). **Do not** freeze.

Using your automated mini-doser and prefilled cartridge

- It is important that you do not try to give yourself the injection unless you have received training from your healthcare provider.
- Adult supervision is recommended for children ages 12 and 13 while using the automated mini-doser and prefilled cartridge.
- **Do not** use the automated mini-doser and prefilled cartridge after the expiration date on the carton.
- **Do not** shake the automated mini-doser or prefilled cartridge.
- **Do not** remove the automated mini-doser and prefilled cartridge from the carton or clear tray until you are ready to inject.
- **Do not** touch the start button until you place the loaded automated mini-doser and prefilled cartridge onto your skin and are ready to inject.
- You can only press the start button once. If an error occurs, the automated mini-doser cannot be used.
- **Do not** use the automated mini-doser and prefilled cartridge if either have been dropped onto a hard surface. Part of the automated mini-doser and prefilled cartridge may be broken even if you cannot see the break. Use a new automated mini-doser and prefilled cartridge.
- **Do not** reuse the automated mini-doser and prefilled cartridge. The automated mini-doser and prefilled cartridge are for single use only.
- **Do not** let the automated mini-doser get wet from water or any other liquids. It contains electronics that should not get wet.
- The single use automated mini-doser for subcutaneous injection is intended only for use with the prefilled cartridge.
- Moderate physical activities can be performed during the injection process, such as walking, reaching and bending.

A healthcare provider who knows how to use the automated mini-doser should be able to answer your questions. For more information, contact the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

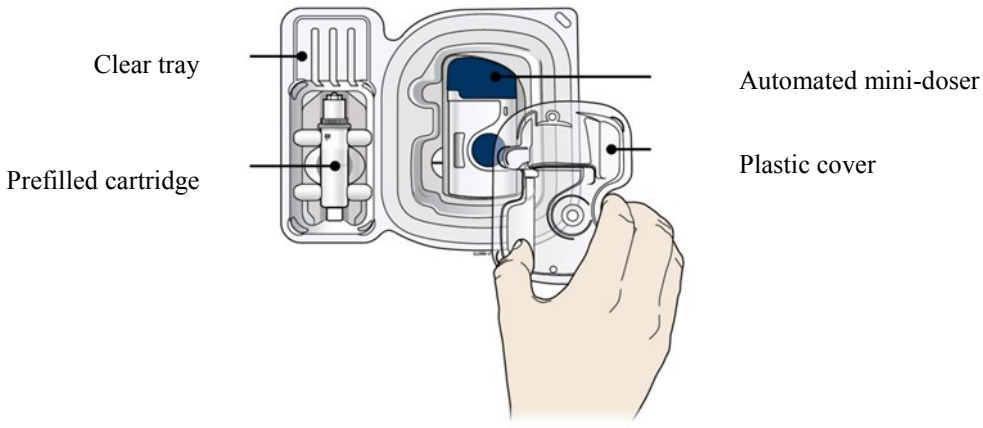
Step 1: Prepare

A. Remove the automated mini-doser and prefilled cartridge carton from the refrigerator. Wait 45 minutes.

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

- **Do not** try to warm the prefilled cartridge by using a heat source such as hot water or a microwave

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



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

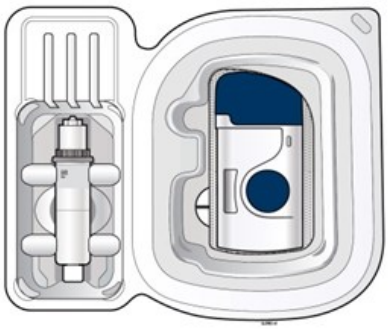
- **Do not** touch the start button until the automated mini-doser is on skin and you are ready to inject.
- **Do not** use if the white paper cover is missing or damaged.

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

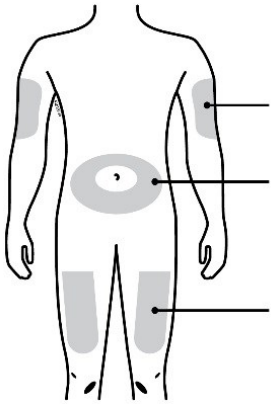
On a clean, well-lit surface, place the:

- Clear tray containing the automated mini-doser and prefilled cartridge
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage

- Sharps disposal container



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



You can use:

- Thigh
- Belly, except for a **five** centimeter (two inch) area around your belly button
- Outer area of upper arm (only if someone else is giving you the injection)

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

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

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

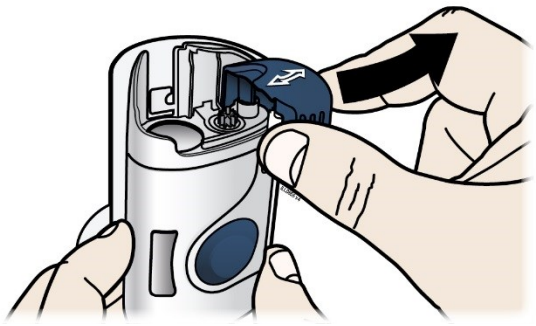
Step 2: Get ready

E. Open the automated mini-doser by swinging the cartridge door to the right. Then**, leave the door open. Do not** close the cartridge door before the cartridge is loaded.

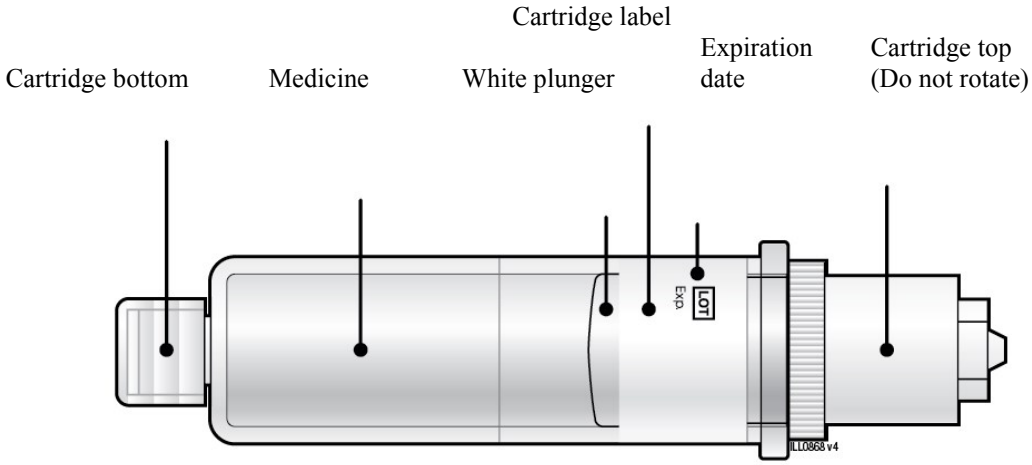
If you accidentally close the cartridge door, press on the left side of the door to release the door latch.

If you are still unable to open the door, call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

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



F. Inspect the cartridge.

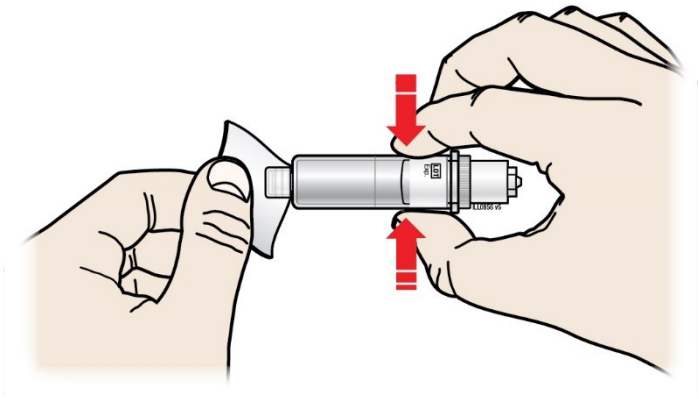


Make sure the medicine in the cartridge is clear and colourless to slightly yellow.

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

In any above cases, use a new automated mini-doser and prefilled cartridge and call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

G. Clean the cartridge bottom.

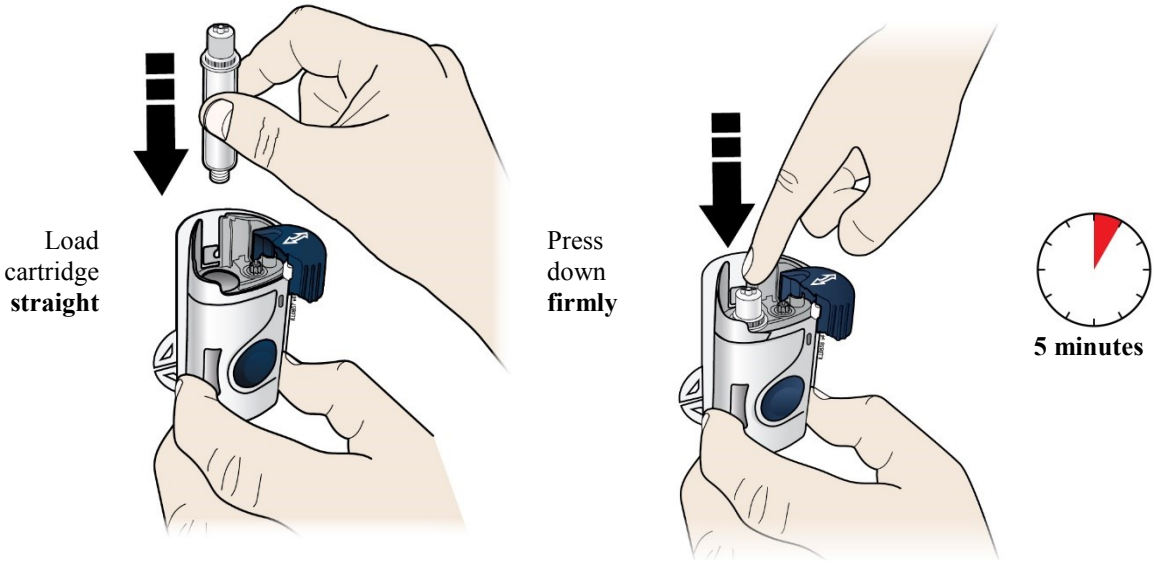


Grab Here

Hold the cartridge barrel and clean the cartridge bottom with an alcohol wipe.

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

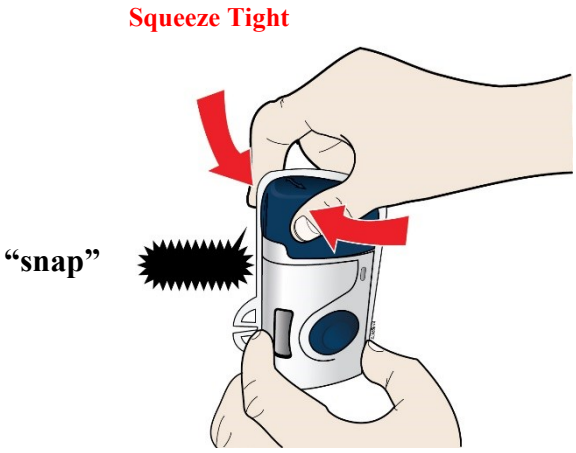
H. Load the cleaned cartridge into the automated mini-doser and firmly press on the top until it is secured in place. **Do not** insert the cartridge more than five minutes before injection. This can dry out the medicine.



Insert the cartridge bottom first.

- **Do not** touch the start button until you have placed the loaded automated mini-doser on your skin

I. Swing the door to the left. Then, squeeze firmly until it snaps shut. Apply enough pressure when closing the door and make sure there is a "snap" before going to the next step.



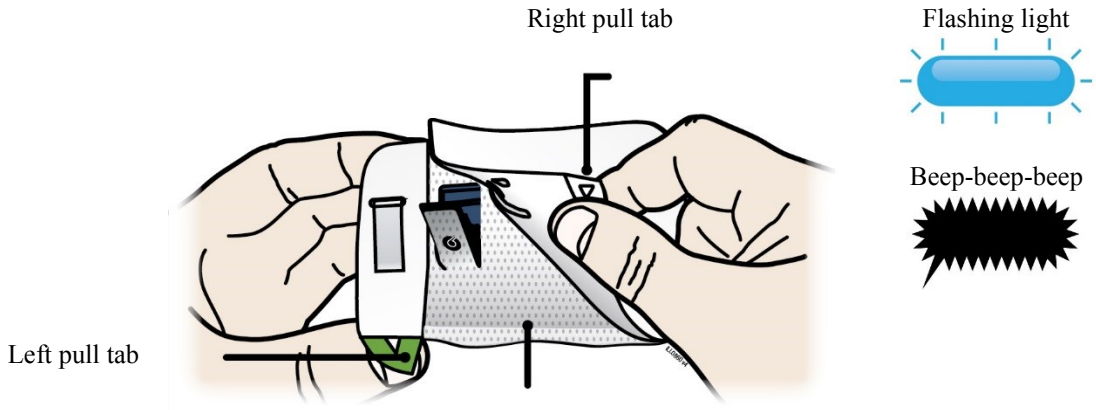
Make sure the cartridge fits securely in the automated mini-doser before you close the door.

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

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

Step 3: Inject

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



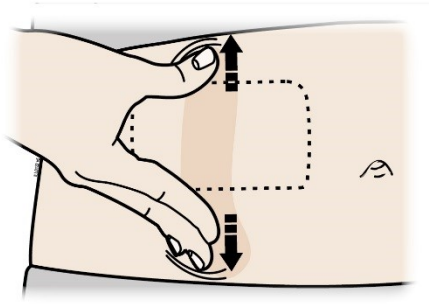
You must remove **both** green pull tabs to turn the loaded automated mini-doser on. You will hear beeping and see a flashing blue status light.

- **Do not** touch the skin adhesive
- **Do not** touch the start button until you have placed the loaded automated mini-doser on your skin

- **Do not** touch or contaminate the needle cover area
- **Do not** place the loaded automated mini-doser on your body if the red status light flashes continuously
- **Do not** pull the skin adhesive backing off of the automated mini-doser
- **Do not** fold the skin adhesive over onto itself

K. Choose your automated mini-doser injection site. Only use the outer arm if someone else is giving the injection.

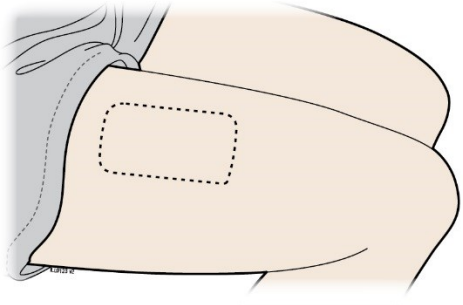
Stomach area placement



Stretch method for belly

OR

Thigh placement

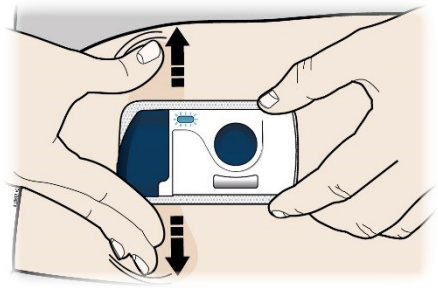


Do not stretch for thigh

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

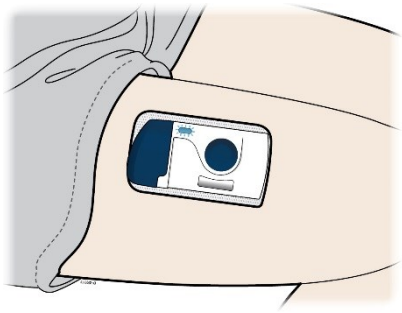
L. When the blue light flashes, the automated mini-doser is ready. **Keep** the **stretch** (stomach area method only). Hold the loaded automated mini-doser with the blue light visible, and place it on your skin. You may hear beeps.

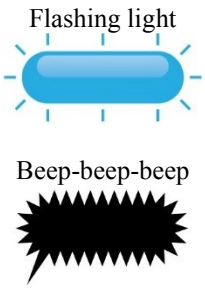
Stomach area placement



OR

Thigh placement



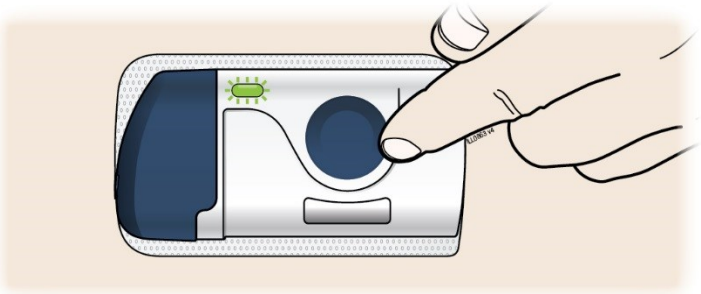


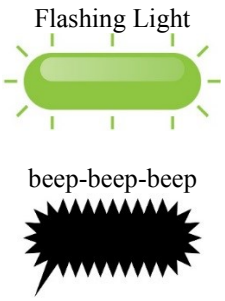
The loaded automated mini-doser will lay flat on your body. Make sure all of the adhesive is attached to your skin. Run a finger around the adhesive edges to secure it.

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

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

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

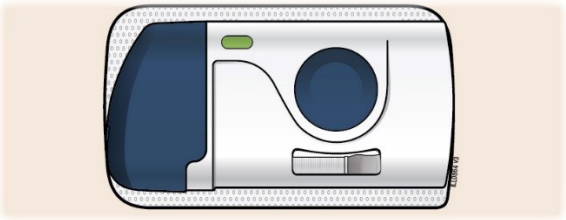


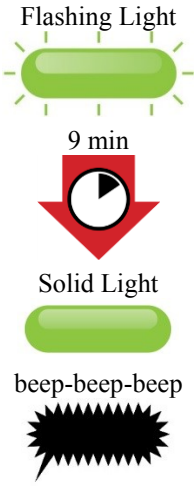


- You may hear a pumping sound.
- You may feel a pinch.
- Make sure you see a green, flashing status light.
- You may hear beeps indicating your injection has started.

Important: If medication leaks from the loaded automated mini-doser, call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

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





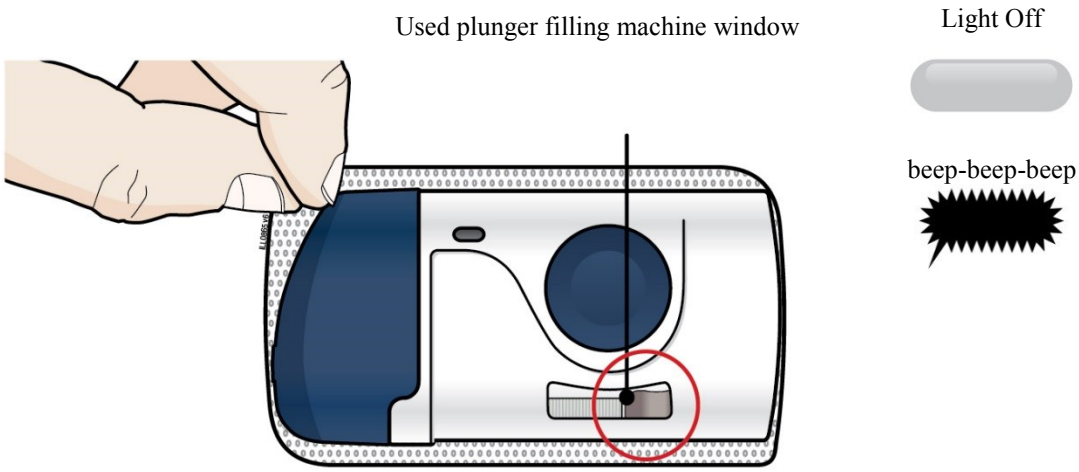
It is okay to hear a pumping sound start and stop during injection.

Injection is finished when:

- The status light changes to **solid green**.
- You hear several beeps.
- The plunger fills the medicine window.

Step 4: Finish

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



Check to see that the used plunger completely fills the medicine window, and the green solid light is turned off, letting you know all medicine has been injected. If the plunger did not fill the window, call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

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

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

The automated mini-doser contains batteries, electronics, and a needle.

Put the used automated mini-doser in a sharps disposal container right away after use. **Do not** throw away (dispose of) the automated mini-doser in your household trash.

If you do not have a sharps disposal container, you may use a household container that is:

- Made of a heavy-duty plastic,
- Can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- Upright and stable during use,
- Leak-resistant, and
- 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 provincial or local laws about how you should throw away used needles and syringes.

- **Do not** remove the used cartridge from the automated mini-doser.
- **Do not** reuse the automated mini-doser.

Do not recycle the automated mini-doser or sharps disposal container or throw them into household trash.

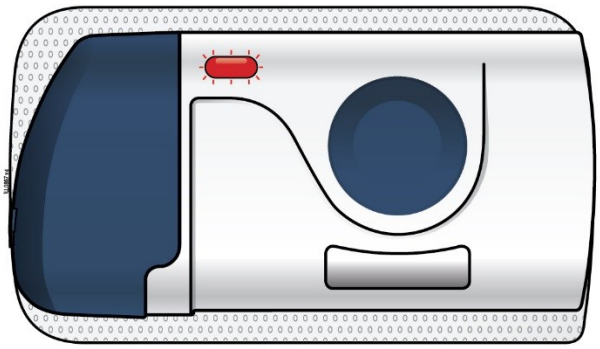
Important: Always keep the sharps disposal container out of the reach of children.

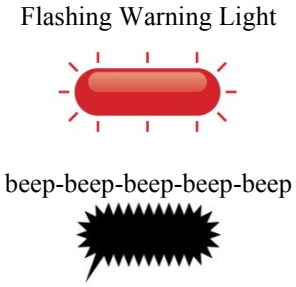
Q. Examine injection site.

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

Troubleshooting:

What do I do if the loaded automated mini-doser status light continuously flashes red and I hear beeps?





Stop using the loaded automated mini-doser. If the automated mini-doser is attached to your body, carefully remove it. Call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

Commonly Asked Questions:

What if I hear the automated mini-doser beep and see a red blinking light when it is on my body?

This means that an error has occurred. When this happens, the injection will automatically stop. Remove the automated mini-doser from your body by slowly and carefully peeling it off of your skin, call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

What should I do if the automated mini-doser comes off my body during the injection?

Though unlikely, if the automated mini-doser comes off during the injection, the automated mini-doser will make a beeping sound, you will see the blinking red light, and the automated mini-doser will stop. The loaded automated mini-doser can no longer be used, and do not reapply to your body. Call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

What if I push the start button before I place the automated mini-doser on my skin?

If you have removed the adhesive backing and pressed the start button, the automated mini-doser will make a beeping sound and you will see the blinking red light. The automated mini-doser will not inject. Stop using the automated mini-doser, call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

What if the automated mini-doser does not beep and the blue status light does not blink when I remove the pull tabs?

Check to see if both green pull tabs have been fully removed from the automated mini-doser, including the adhesive paper over the battery strip and needle cover. If both green pull tabs have been fully removed and the automated mini-doser still does not turn on, use a new automated mini-doser and prefilled cartridge. Call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

What if I push the start button and nothing happens?

Remove the automated mini-doser by slowly and carefully peeling it away from your skin. Do not reapply the same automated mini-doser that you have already placed on your skin. Call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

What if I cannot open the cartridge door to insert the cartridge?

To open the automated mini-doser door, press on the left side of the door to release the door latch. If you are still unable to open the door, call 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

Additional environmental conditions:

Relative humidity range is 15% to 85%.

Altitude range is -300 meters to 3500 meters.

During injection, keep the automated mini-doser a minimum of 10 cm (4 inches) away from other electronics such as cellular phones.

Warning: Do not modify the device.

Automated mini-doser operating temperature range is 15°C to 40°C.

www.devicepatents.com

SYMBOL TABLE				
 Do not re-use	 Serial number	 Type BF Applied Part	 Do not use if packaging is damaged	 Automated mini-doser containing 420 mg/3.5 mL (120 mg/mL)
 Sterilized using ethylene oxide	 Refer to Instructions for Use	 Lot number	 Keep dry	 Open here

Usual Dose:

Prevention of Cardiovascular Events and Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The usual dose for REPATHA is 140 mg every 2 weeks or 420 mg once monthly. If you and your doctor have decided that you should switch from one dosing regimen to the other, take the first dose of the new regimen on the day you were scheduled to take the previous one.

Homozygous Familial Hypercholesterolemia

The usual dose for REPATHA is 420 mg, either once monthly or every 2 weeks. If you are on apheresis you may initiate treatment with 420 mg every 2 weeks to correspond with your apheresis schedule.

Overdose:

If you think you have taken too much REPATHA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your every 2 week or once monthly dose of REPATHA or are not able to take the dose at the regular time, administer your missed dose as soon as you remember, as long as there are more than 7 days until your next scheduled dose. If there are 7 days or less until your next scheduled dose, administer the next dose according to the original schedule. This will put you back on your original schedule. If you are not sure when to take REPATHA after a missed dose, ask your healthcare provider or pharmacist.

What are possible side effects from using REPATHA:

Like all medicines, REPATHA can cause side effects, although not everybody gets them. REPATHA may cause allergic reactions. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction including a severe rash, redness, severe itching, a swollen face or trouble breathing. The following are possible side effects when taking REPATHA. If you experience any side effects not listed here, or if any side effect becomes bad enough to interfere with your daily activities, contact your healthcare professional.

- Flu or flu-like symptoms (high temperature, sore throat, runny nose, cough and chills)
- Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections)
- Nausea
- Back pain
- Joint pain (arthralgia)
- High blood sugar levels (diabetes)

- Injection site reactions (redness, bruising, pain, swelling, or bleeding)
- Allergic reactions including rash, hives, red itchy bumps on your skin (urticaria), and in rare cases, swelling of face, mouth, tongue or throat (angioedema)

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect®;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect® http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store in a refrigerator at 2°C to 8°C in the original carton. When removed from the refrigerator, REPATHA should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days. Protect REPATHA from direct light and do not expose to temperatures above 25°C. Do not freeze. Do not shake.

Keep REPATHA and all medicines out of the reach from children.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use.

If you want more information about REPATHA:

Talk to your healthcare professional.

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842) or by visiting www.repatha.ca.

This leaflet was prepared by Amgen Canada Inc.

Last Revised: February 27, 2019

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrREPATHA®
(evolocumab)

Single-use Prefilled Syringe*

Read this carefully before you start taking REPATHA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REPATHA. Keep this leaflet, as you may need to read it again.

What is REPATHA used for?

REPATHA is used:

- along with diet and in combination with usual therapy, including cholesterol-lowering medications called statins, to reduce the risk of heart attack, stroke, and certain heart procedures (to restore blood flow to the heart) in adult patients who have cardiovascular disease.
- alone or together with other cholesterol-lowering medicines, along with diet, in adults with primary hyperlipidemia (high cholesterol level in your blood) to reduce LDL cholesterol.
- along with diet and other LDL lowering therapies in people with homozygous familial hypercholesterolemia 12 years and older (an inherited condition that causes high levels of LDL), who need additional lowering of LDL cholesterol.

It is not known if REPATHA is safe and effective in children with homozygous familial hypercholesterolemia (HoFH) who are younger than 12 years of age or in children with primary hyperlipidemia who are younger than 18 years of age.

How does REPATHA work?

REPATHA is a medicine used to lower levels of cholesterol. REPATHA lowers levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, REPATHA raises levels of "good" cholesterol (HDL cholesterol).

Evolocumab, the active ingredient of REPATHA, works by helping the liver's ability to remove bad cholesterol from the blood. Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol. LDL cholesterol is often called "bad" cholesterol because it can build up in the walls of your arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke and can cause other health problems. HDL cholesterol is often called "good" cholesterol because it helps keep the bad cholesterol from

*Prefilled syringes are not available in Canada

building up in the arteries and protects against heart disease. Triglycerides are another form of fat in your blood that may increase your risk of heart disease.

What are the ingredients in REPATHA?

The active substance is evolocumab.

- Each 1 mL prefilled autoinjector contains 140 mg of evolocumab (140 mg/mL)
- Each 3.5 mL prefilled cartridge contains 420 mg of evolocumab (120 mg/mL)
- Each 1 mL prefilled syringe* contains 140 mg of evolocumab (140 mg/mL)

The other ingredients are proline, glacial acetic acid, polysorbate 80, water for injection, sodium hydroxide.

REPATHA comes in the following dosage forms:

REPATHA is available in the presentations listed below. Your doctor will prescribe the type that is best for you.

- 140 mg/mL 1 mL single-use prefilled autoinjector (SureClick®)
- 120 mg/mL 3.5 mL prefilled cartridge with an automated mini-doser (AMD)
- 140 mg/mL 1 mL single-use prefilled syringe*

Do not use REPATHA if:

You should not take REPATHA if you have ever had an allergic reaction to REPATHA or any of the ingredients in REPATHA.

To help avoid effects and ensure proper use, talk to your healthcare professional before you take REPATHA. Talk about any health conditions or problems you may have.

If you use REPATHA together with a statin and other cholesterol lowering medicines, please read the package leaflet of that particular medicine.

If you have allergies, or 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. There is no dry natural rubber in the automated mini-doser with prefilled cartridge.

Children and adolescents

The use of REPATHA has not been studied in children under 18 years of age being treated for primary hyperlipidemia. The use of REPATHA has not been studied in children under 12 years of age being treated for homozygous familial hypercholesterolemia.

Other Medicines and REPATHA

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

*Prefilled syringes are not available in Canada

Pregnancy and Breastfeeding

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

If you are trying to get pregnant or think you may be pregnant when taking REPATHA:

- Inform your doctor
- If you are also taking a statin along with REPATHA, stop taking REPATHA and read the package leaflet of the statin that you are taking with REPATHA

If you become pregnant while taking REPATHA, talk to your healthcare provider about registering in the pregnancy exposure registry for REPATHA. You can enroll in this registry by calling 1-877-311-8972 or by visiting https://mothertobaby.org/ongoing-study/repatha/. The purpose of this registry is to collect information about the safety of REPATHA during pregnancy.

It is not known whether REPATHA is found in breast milk. It is important to tell your doctor if you are breastfeeding or plan to do so. Your doctor will then help you decide whether to stop breastfeeding, or whether to stop taking REPATHA, considering the benefit of breastfeeding to the baby and the benefit of REPATHA to the mother.

How to take REPATHA:

REPATHA is given as an injection under the skin (subcutaneous or SC). REPATHA is available in the presentations listed below. Your doctor will prescribe the type that is best for you.

- Single-use prefilled autoinjector (SureClick®)
- Single-use automated mini-doser
- Single-use prefilled syringe*

If your doctor decides that you or a caregiver can give the injections of 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.

Always take REPATHA exactly as your doctor has told you. Check with your doctor if you are not sure.

- Before starting REPATHA, you should be on a diet to lower your cholesterol.
- You should stay on this cholesterol lowering diet while taking REPATHA.

If your doctor has prescribed REPATHA along with a statin or other cholesterol lowering medicine, follow your doctor's instructions on how to take these medicines together. In this case, please read the dosage instructions in the package leaflet of the other medicines.

Ask your doctor if you have any further questions on how to use REPATHA

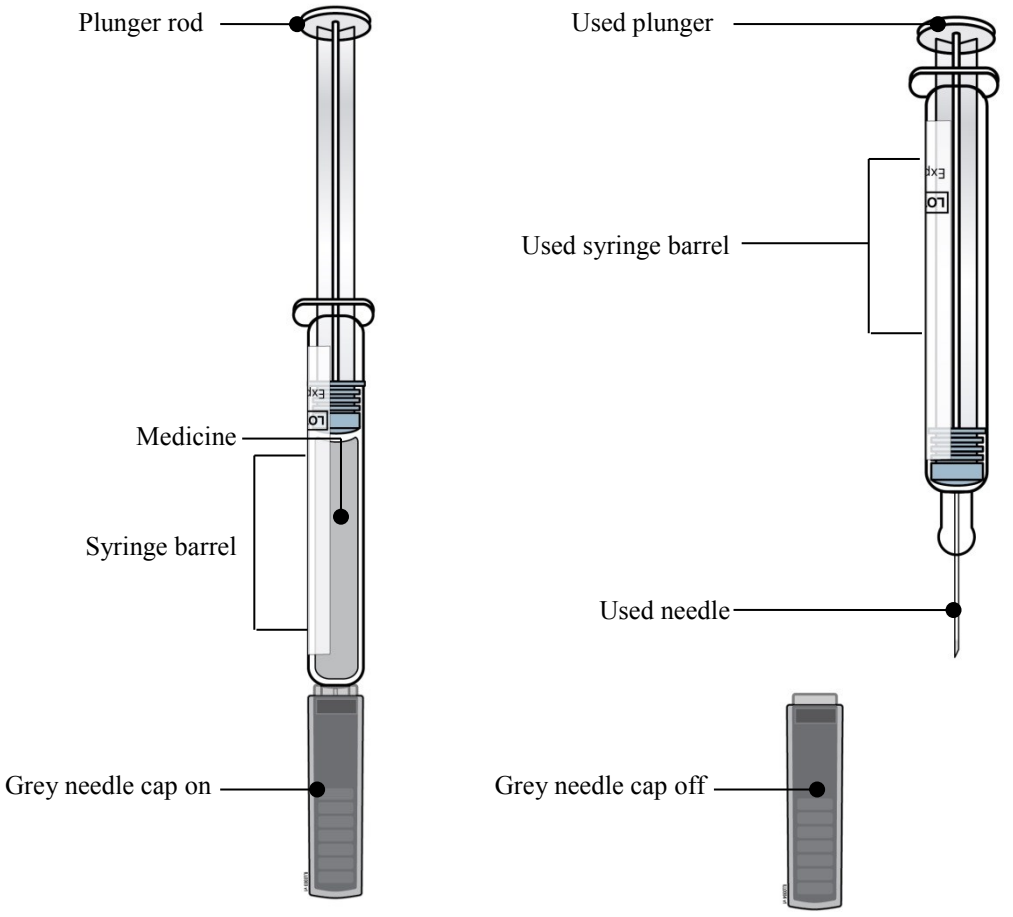
*Prefilled syringes are not available in Canada

REPATHA Single-Use Prefilled Syringe*:

The following instructions are for preparing and giving an injection of REPATHA using a single-use prefilled syringe*.

Guide to Parts

Before use **After use**



Needle is inside

Important

Before you use a Single-Use REPATHA Prefilled Syringe*, read this important information:

- Keep the REPATHA prefilled syringe* in the original carton to protect from light during storage.
- The REPATHA prefilled syringe* should be kept in the refrigerator between 2°C to 8°C.

*Prefilled syringes are not available in Canada

- It is important that you do not try to give yourself the injection unless you have received training from your healthcare provider.
- The grey needle cap on the REPATHA prefilled syringe* is composed of dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.
- Keep the REPATHA prefilled syringe* out of the sight and reach of children.

✘ **DO NOT:**

- Use the REPATHA prefilled syringe* if the packaging is open or damaged.
- Freeze the REPATHA prefilled syringe* or use one that has been frozen.
- Use the REPATHA prefilled syringe* if it has been dropped onto a hard surface. Part of the REPATHA prefilled syringe* may be broken even if you cannot see the break. Use a new REPATHA prefilled syringe*.
- Remove the grey needle cap from the REPATHA prefilled syringe* until you are ready to inject.

A healthcare provider familiar with REPATHA should be able to answer your questions. For more information, contact the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842) or visit www.repatha.ca.

Step 1: Prepare

A. Remove the REPATHA prefilled syringe* carton from the refrigerator and wait 30 minutes.

Wait at least 30 minutes for the prefilled syringe* in the carton to naturally reach room temperature before injecting.

Check that the name REPATHA appears on the carton label.

✘ **DO NOT:**

- Try to warm the REPATHA prefilled syringe* by using a heat source such as hot water or microwave.
- Leave the REPATHA prefilled syringe* exposed to direct sunlight.
- Shake the REPATHA prefilled syringe*.

B. Gather all materials needed for your injection.

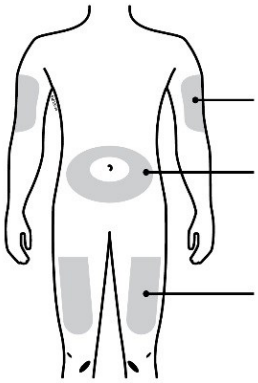
Wash your hands thoroughly with soap and water. **On a clean, well-lit, flat work surface, place:**

- One REPATHA prefilled syringe* in carton
- Alcohol wipes
- Cotton ball or gauze pad

*Prefilled syringes are not available in Canada

- Adhesive bandage
- Sharps disposal container
- ✘ **DO NOT** use if expiration date on the REPATHA prefilled syringe* carton has passed.

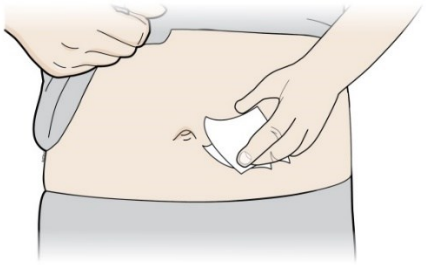
C. Choose your injection site.



You can use:

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

D. Clean your injection site.



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

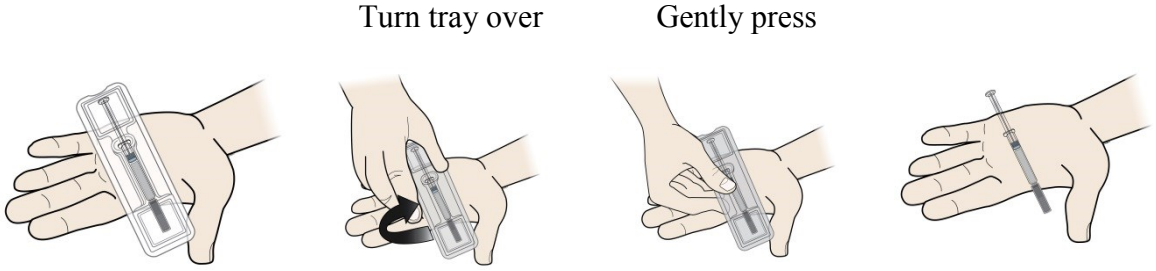
- ✘ **DO NOT** touch this area of skin again before injecting.

Choose a different site each time you give yourself an injection. If you need to use the same injection site, just make sure it is not the same spot on that site you used last time.

*Prefilled syringes are not available in Canada

DO NOT inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

E. Remove prefilled syringe* from tray.



To remove:

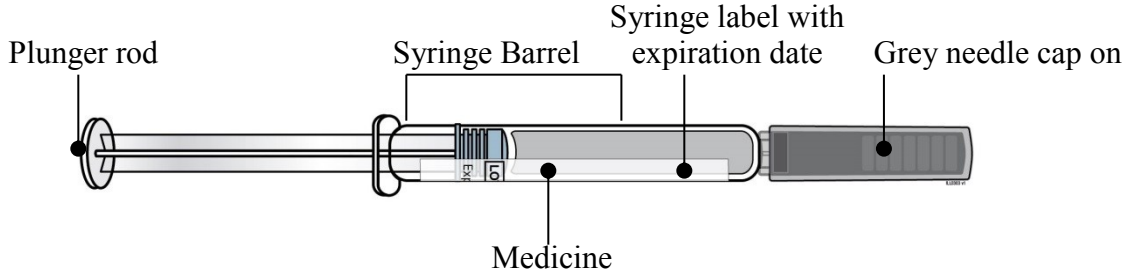
- Peel paper off of tray.
- Place the tray on your hand.
- Turn the tray over and gently press the middle of the tray's back to release the syringe into your palm.
- If prefilled syringe* does not release from tray, gently press on back of tray.

✘ **DO NOT**:

- Pick up or pull the prefilled syringe* by the plunger rod or grey needle cap. This could damage the syringe.
- Remove the grey needle cap from the prefilled syringe* until you are ready to inject.

Always hold the prefilled syringe* by the syringe barrel.

F. Inspect medicine and syringe.



Always hold the prefilled syringe* by the syringe barrel.

*Prefilled syringes are not available in Canada

Check that:

- The name REPATHA appears on the prefilled syringe* label.
- The medicine in the prefilled syringe* is clear and colourless to slightly yellow.

✘ **DO NOT** use the prefilled syringe* if:

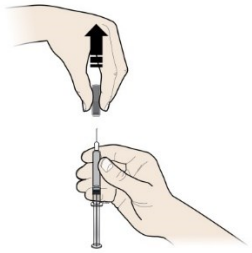
- any part of the prefilled syringe* appears cracked or broken.
- the grey needle cap is missing or not securely attached.
- the medicine is discoloured or contains large lumps, flakes or coloured particles.
- the expiration date on the prefilled syringe* has passed.

In any above cases, use a new prefilled syringe* and contact the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842).

Step 2: Get Ready

A. Carefully pull the grey needle cap straight out and away from your body.

1.



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

2.

Immediately place the cap in the sharps disposal container.

✘ **DO NOT**:

- twist or bend the grey needle cap. This can damage the needle.
- put the grey needle cap back onto the prefilled syringe*.

B. Remove the air bubble/gap.

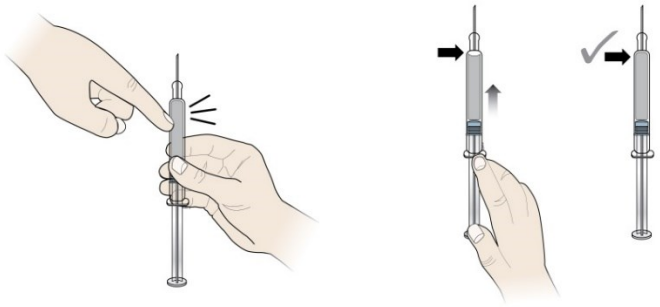
You may notice an air bubble/gap in the REPATHA prefilled syringe*.

If you notice an air bubble/gap:

- Hold the prefilled syringe* with the needle facing up.
- Gently tap the syringe barrel with your fingers until the air bubble/gap rises to the top of the syringe.

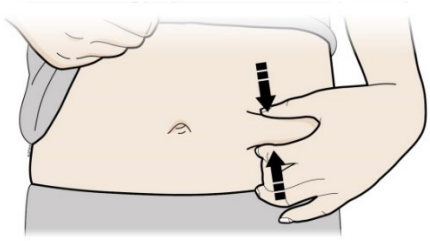
*Prefilled syringes are not available in Canada

- Slowly and gently push the plunger rod up to get the air out of the prefilled syringe*. Be very careful not to push out any medicine.



✘ **DO NOT** tap the syringe needle.

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

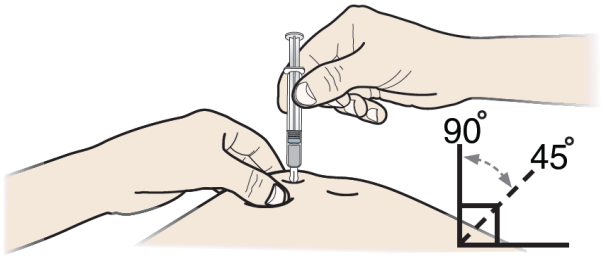


Pinch skin firmly between your thumb and fingers, creating an area about five centimeters (two inches) wide.

It is important to keep the skin pinched while injecting.

Step 3: Inject

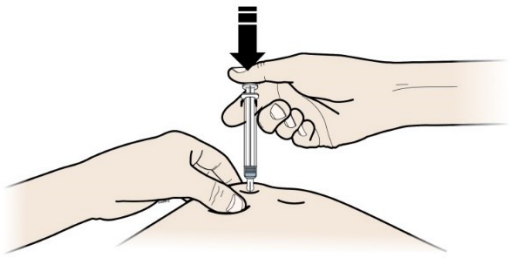
A. Hold the PINCH. Insert the needle into skin using a 45 to 90 degree angle.



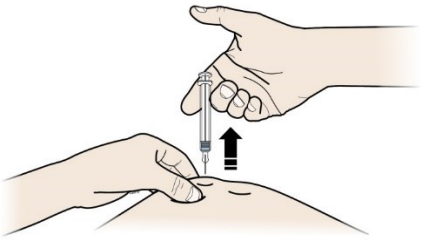
✘ **DO NOT** place your finger on the plunger rod while inserting the needle.

*Prefilled syringes are not available in Canada

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



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



✘ **DO NOT** put the grey needle cap back onto the used syringe.

Step 4: Finish

A. Immediately place the used syringe in a sharps disposal container.

✘ **DO NOT:**

- reuse the used syringe.
- use any medicine that is left in the used syringe.
- recycle the syringe or the sharps disposal container or throw it into household trash.

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

B. Examine the injection site.

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

✘ **DO NOT** rub the injection site

Usual Dose:

Prevention of Cardiovascular Events and Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The usual dose for REPATHA is 140 mg every 2 weeks or 420 mg once monthly. If you and your doctor have decided that you should switch from one dosing regimen to the other, take the first dose of the new regimen on the day you were scheduled to take the previous one.

Homozygous Familial Hypercholesterolemia

The usual dose for REPATHA is 420 mg, either once monthly or every 2 weeks. If you are on apheresis you may initiate treatment with 420 mg every 2 weeks to correspond with your apheresis schedule.

Overdose:

If you think you have taken too much REPATHA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your every 2 week or once monthly dose of REPATHA or are not able to take the dose at the regular time, administer your missed dose as soon as you remember, as long as there are more than 7 days until your next scheduled dose. If there are 7 days or less until your next scheduled dose, administer the next dose according to the original schedule. This will put you back on your original schedule. If you are not sure when to take REPATHA after a missed dose, ask your healthcare provider or pharmacist.

What are possible side effects from using REPATHA:

Like all medicines, REPATHA can cause side effects, although not everybody gets them. REPATHA may cause allergic reactions. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction including a severe rash, redness, severe itching, a swollen face or trouble breathing. The following are possible side effects when taking REPATHA. If you experience any side effects not listed here, or if any side effect becomes bad enough to interfere with your daily activities, contact your healthcare professional.

- Flu or flu-like symptoms (high temperature, sore throat, runny nose, cough and chills)
- Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections)
- Nausea
- Back pain
- Joint pain (arthralgia)

- High blood sugar levels (diabetes)
- Injection site reactions (redness, bruising, pain, swelling, or bleeding)
- Allergic reactions including rash, hives, red itchy bumps on your skin (urticaria), and in rare cases, swelling of face, mouth, tongue or throat (angioedema).

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect®;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect® http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store in a refrigerator at 2°C to 8°C in the original carton. When removed from the refrigerator, REPATHA should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days. Protect REPATHA from direct light and do not expose to temperatures above 25°C. Do not freeze. Do not shake.

Keep REPATHA and all medicines out of the reach from children.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use.

If you want more information about REPATHA:

Talk to your healthcare professional.

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the RepathaReady® Support Program at 1-888-Repatha (1-888-737-2842) or by visiting www.repatha.ca.

This leaflet was prepared by Amgen Canada Inc.

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