PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrREPATHA™

(evolocumab)

Solution for Subcutaneous Injection

140 mg in 1.0 mL (140 mg/mL)

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

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Mississauga, Ontario
L5N 0A4

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[Pr]REPATHA™

(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	proline, glacial acetic acid (acetate), Polysorbate 80, Sodium hydroxide, water for injection *For a complete listing see Dosage Forms, Composition and Packaging section.*

† Pre-filled 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

Primary Hyperlipidemia

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

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

Homozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (eg, 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 6026 total number of patients in clinical studies of REPATHA, 1779 (30%) were ≥ 65 years of age, while 223 (4%) were ≥ 75 years of age. No overall differences in safety or efficacy were observed between these patients and younger patients but data are limited in patients over 75 years of age (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 (eg, 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 contains dry natural rubber, which is a derivative of latex. This may cause an allergic reaction in latex-sensitive patients.

Immune

Hypersensitivity reactions (eg, rash, urticaria) have been reported in patients treated with REPATHA, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with REPATHA 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 placenta 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 is used in combination with maximally tolerated statin. 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.

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 6026 total number of patients in clinical studies of REPATHA, 1779 (30%) were ≥ 65 years of age and 223 (4%) were ≥ 75 years of age. No overall differences in safety or efficacy were observed between these patients and younger patients but data are limited in patients over 75 years of age.

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:

The safety and efficacy of REPATHA in patients with severe renal impairment, including end-stage renal disease, have not been studied. The use of REPATHA in patients with severe renal impairment is not recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of REPATHA was evaluated in approximately 6700 patients with primary hyperlipidemia and mixed dyslipidemia; 4971 patients received REPATHA, representing 4242 patient-years of exposure of REPATHA at doses of 140 mg every two weeks and 420 mg every month. Adverse events leading to discontinuation of REPATHA occurred infrequently and only nausea (0.2%) was reported at a greater rate than control (0.1%). The most common adverse

reactions with REPATHA reported in > 2% of patients and greater than control were nasopharyngitis, upper respiratory tract infection, influenza, back pain, arthralgia and nausea. Rash, urticaria and injection site reactions have also been reported.

Serious adverse events were reported in 2.8% of patients treated with REPATHA vs. 2.1% in any control group with no system organ class reported in greater than 1.0% of patients.

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 Patients with Primary Hyperlipidemia and in Patients with 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 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		
Diarrhoea	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 Eight Pooled Controlled Trials (Seven 12-week Trials and One 52-Week Trial)

The adverse reactions described below are from a pool of the 52-week trial 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.

Allergic Reactions

Hypersensitivity events were reported in 5.1% and 4.6% of REPATHA-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for REPATHA and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%) (see WARNINGS AND PRECAUTIONS, Immune).

Injection Site Reactions

Injections site reactions have been reported in patients treated with REPATHA (3.2% REPATHA-treated vs. 3.0% placebo). The most common injection site reactions were erythema, pain and bruising. 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 0.0% in the control group. The proportions of patients who experienced recurrent local injection site reactions were 1.2% in the REPATHA group and 0.5% in the control group.

Neurocognitive Events

The rates of neurocognitive events in the placebo-controlled trials reported wereless than or equal to 0.2% in REPATHA-treated and placebo-treated patients. Most of the neurocognitive events were non-serious and most were mild or moderate in severity.

Musculoskeletal Events

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

LDL Levels

In an integrated analysis of phase 2 and 3 double-blind, randomized placebo and active controlled studies of REPATHA, adverse events were reported in 51% (N = 1609) of patients in the REPATHA group who achieved an LDL-C < 0.6 mmol/L and 51% (N = 2565) of patients in the REPATHA group who achieved an LDL-C < 1.0 mmol/L compared to 52% (N = 1339) of patients in the REPATHA group with an LDL-C ≥ 1.0 mmol/L and 50% (N = 2038) of patients in the control group with LDL-C ≥ 1.0 mmol/L. Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by REPATHA are unknown.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS: *Anaemia (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), Oedema 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: *Paraesthesia (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, 0.1% of patients (7 out of 4846) treated with at least one dose of REPATHA tested positive for binding antibody development (4 of these patients had transient antibodies). The patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies and none of the patients tested positive for neutralizing antibodies.

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

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.

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

Primary Hyperlipidemia

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

One prefilled syringe† (PFS) or prefilled autoinjector (AI) delivers the 140 mg every 2 week dose, and 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. 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.

Patients with Renal Impairment

No dosage adjustment is necessary in patients with mild to moderate 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

Patients who miss a dose of REPATHA should be advised to take REPATHA as soon as possible after the missed dose and to contact their doctor to find out when to take next dose.

Administration

Prior to subcutaneous administration, allow REPATHA to sit at room temperature up to 25°C for at least 30 minutes. 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.

[†] Pre-filled syringes are not available in Canada

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.

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 (tmax) 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 (Cmax) and total exposure (AUClast), 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 in patients with mild or moderate renal impairment relative to non-renally impaired patients. Patients with severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 mLs/min/1.73m^2) have not been studied.

STORAGE AND STABILITY

REPATHA prefilled syringes † and autoinjectors 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.

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.
- 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.

[†] Pre-filled 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

Heterozygous Familial Hypercholesterolemia

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.

In these patients with HeFH on statins with or without other lipid lowering therapies, 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 3.

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

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 (95% CI)	-61* (-67, -55)	-55* (-60, -49)	-49* (-55, -44)	-41 (-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 (95% CI)	-60* (-68, -53)	-55* (-62, -48)	-49* (-56, -43)	-40 (-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

Primary Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease

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
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	1896	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

Q2W = once every 2 weeks; QM = once monthly; QD = once daily, SC = subcutaneously, PO = oral, SoC = standard of care.

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 296 patients with atherosclerotic CVD who received REPATHA or placebo as add-on therapy to daily doses of atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg. Among these patients, the mean age at baseline was 63 years (range: 32 to 80 years), 45% were ≥ 65 years old, 33% were women, 98% were White, 2% were Black, <1% were Asian and 5% were Hispanic or Latino. After 4 weeks of statin therapy, the mean baseline LDL-C was 2.8 mmol/L.

DESCARTES was an international, multicentre, double-blind, randomized, placebo-controlled, 52-week trial that included 139 patients with atherosclerotic CVD 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 59 years (range, 35 to 75 years), 25% were ≥ 65 years, 40% were women, 80% were White, 3% were Black, 5% were Asian, and <1% were Hispanic or Latino. After stabilization on the assigned background therapy, the mean baseline LDL-C was 2.7 mmol/L.

Study Results

In the LAPLACE-2 study for these patients with atherosclerotic CVD who were on maximum-dose statin therapy, the overall difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -74% (95% CI: -84%, -64%; $p < 0.0001$) and -63% (-76%, -50%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For individual results see Table 5.

Table 5. Effect of REPATHA on Lipid Parameters in Patients with Atherosclerotic CVD on Atorvastatin 80 mg, Rosuvastatin 40 mg, or Simvastatin 40 mg (Mean % Change from Baseline to Week 12)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Background Treatment with Atorvastatin 80 mg				
Placebo every 2 weeks (n = 14)	0	2	9	2
REPATHA 140 mg every 2 weeks† (n = 34)	-71	-59	-47	-42
Mean difference of REPATHA from placebo (95% CI)	-71* (-94, -49)	-61* (-81, -42)	-56* (-71, -41)	-44 (-60, -27)
Placebo once monthly (n = 17)	9	6	-2	3
REPATHA 420 mg once monthly† (n = 41)	-62	-51	-53	-34
Mean difference from placebo (95% CI)	-70* (-90, -51)	-56* (-72, -40)	-51* (-65, -37)	-37 (-48, -25)
Background Treatment with Rosuvastatin 40 mg				
Placebo every 2 weeks (n = 11)	10	8	4	5
REPATHA 140 mg every 2 weeks† (n = 30)	-64	-57	-51	-37
Mean difference of REPATHA from placebo (95% CI)	-74* (-91,-57)	-64* (-79, -49)	-55* (-68, -42)	-41 (-51, -31)
Placebo once monthly (n = 13)	3	5	3	3
REPATHA 420 mg once monthly† (n = 33)	-59	-46	-45	-32
Mean difference of REPATHA from placebo (95% CI)	-62* (-89, -35)	-51* (-72, -31)	-48* (-65, -31)	-35 (-50, -20)
Background Treatment with Simvastatin 40 mg				
Placebo every 2 weeks (n = 17)	16	7	6	7
REPATHA 140 mg every 2 weeks† (n = 41)	-59	-51	-49	-37
Mean difference of REPATHA from placebo (95% CI)	-75* (-90, -60)	-59* (-71, -46)	-56* (-66, -45)	-44 (-53, -34)
Placebo once monthly (n = 14)	-4	4	-1	0
REPATHA 420 mg once monthly† (n = 31)	-59	-50	-49	-35
Mean difference of REPATHA from placebo (95% CI)	-55* (-77, -32)	-54* (-73, -35)	-48* (-66, -30)	-35 (-49, -21)

[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 DESCARTES study for these patients with atherosclerotic CVD on maximum-dose atorvastatin therapy with or without ezetimibe, the overall difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -57 % (95% CI: -61%, -46%; $p < 0.0001$). For individual results see Table 6.

Table 6. Effect of REPATHA on Lipid Parameters in Patients with Atherosclerotic CVD on Atorvastatin 80 mg with or without Ezetimibe 10 mg daily (Mean % Change from Baseline to Week 52)

Treatment Group	LDL-C[a]	Non-HDL-C	Apo B	Total Cholesterol
Background Treatment with Atorvastatin 80 mg				
Placebo once monthly (n = 13)	5	5	4	5
REPATHA 420 mg once monthly (n = 30)	-63	-49	-49	-32
Mean difference of REPATHA from placebo (95% CI)	-68* (-85, -50)	-54* (-70, -39)	-53* (-67, -39)	-37* (-47, -26)
Background Treatment with Atorvastatin 80 mg and Ezetimibe 10 mg				
Placebo once monthly (n = 31)	3	4	0	3
REPATHA 420 mg once monthly (n = 65)	-50	-42	-39	-29
Mean difference of REPATHA from placebo (95% CI)	-53* (-67, -39)	-46* (-59, -34)	-40* (-51, -28)	-32* (-42, -23)

[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.

Homozygous Familial Hypercholesterolemia

Study Demographics and Trial Design

Table 7. 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 Q2W	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 (eg, 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 (TESLA)

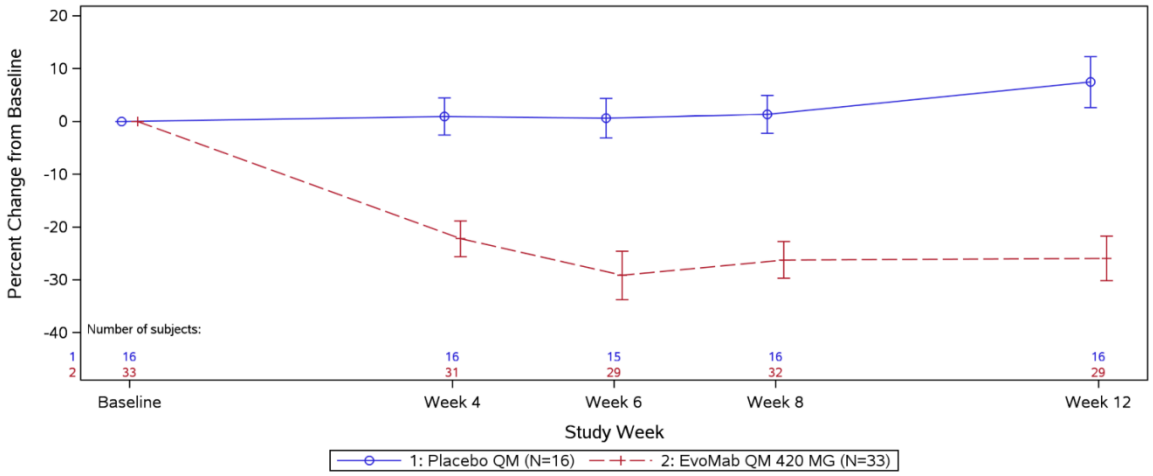
In Part B of TESLA, REPATHA 420 mg once monthly significantly reduced LDL-C at week 12 as compared with placebo: mean percent change from baseline to Week 12 was -32% (95% CI: -45%, -19%; p<0.001). For additional information see Table 8.

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

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 1. 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 (TAUSSIG)

Based on interim study results, long-term use of REPATHA demonstrated a sustained treatment effect as evidenced by reduction of LDL-C of in patients with HoFH (overall, non-apheresis, apheresis) (Table 9). 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 9. Effect of REPATHA on LDL-C in Patients with HoFH – Mean Percent Change from Baseline to OLE Week 36

Patient Population (N)	OLE Week 12	OLE Week 24	OLE Week 36
HoFH (N = 96)	-20 (n = 70)	-23 (n = 46)	-24 (n = 30)
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	-21
Range	-92, 38	-58, 46	-10

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 (ie, 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 were 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.

What is REPATHA used for?

REPATHA is used:

- along with diet and maximally tolerated statin therapy in adults with primary hyperlipidemia or who have clinical atherosclerotic cardiovascular disease, such as heart attacks or strokes, who need additional lowering of 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.

The effect of REPATHA on heart problems such as heart attacks, stroke, or death is not known.

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 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®)
- 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.

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

Pregnancy and Breast-feeding

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

† Pre-filled syringes are not available in Canada

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

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

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

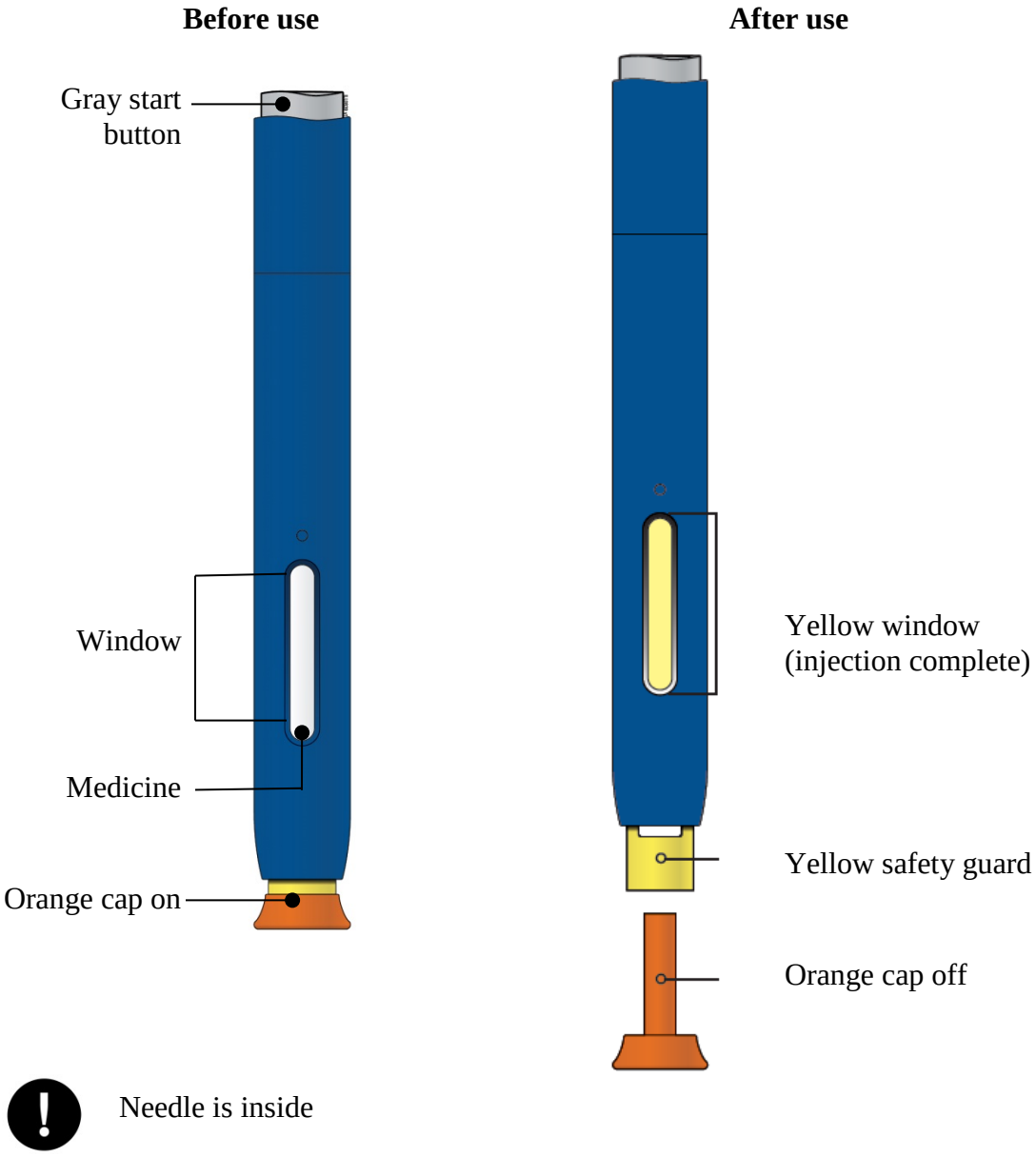
Ask your doctor if you have any further questions on how to use REPATHA.

† Pre-filled 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



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.
- shake the REPATHA SureClick® autoinjector.
- remove the orange cap from the REPATHA SureClick® autoinjector until you are ready to inject.
- 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.
- 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
- leave the autoinjector in direct sunlight
- shake the autoinjector
- remove the orange cap from the autoinjector yet

B. Inspect the REPATHA SureClick® autoinjector.

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

Check the expiration date.

✘ **DO NOT** use autoinjector if:

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

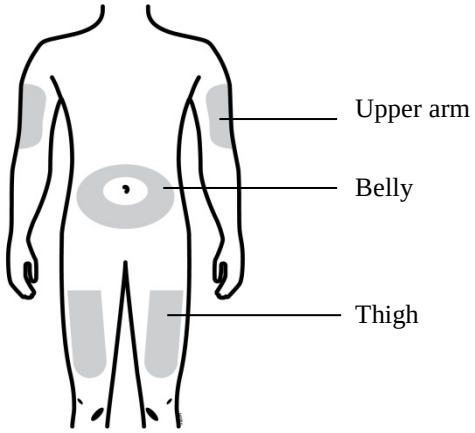
In all cases, use a new autoinjector, and contact the RepathaReady™ Support Program at 1-888-Repatha (1-888-737-2842).

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 2 inch (5 centimeter) 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.

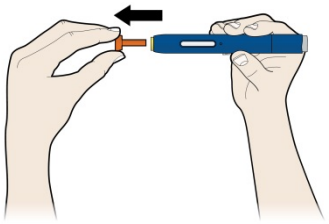
✘ **DO NOT** touch this area again before injecting

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 when you are ready to inject.



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

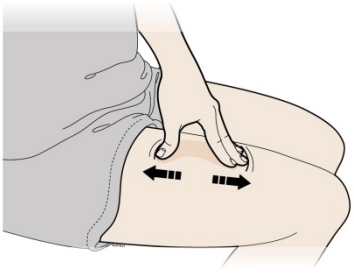
✘ **DO NOT:**

- twist, bend or wiggle the orange cap
- put the orange cap back onto the autoinjector
- put fingers into the yellow safety guard

DO NOT remove the orange cap from the autoinjector until you are ready to inject.

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

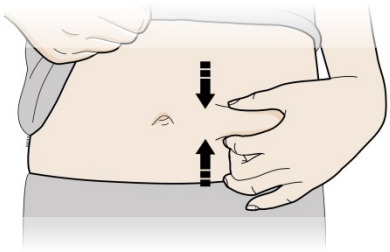
Stretch Method



Stretch skin firmly by moving your thumb and fingers in opposite directions, creating an area about 2 inches (5 centimeters) wide.

OR

Pinch method

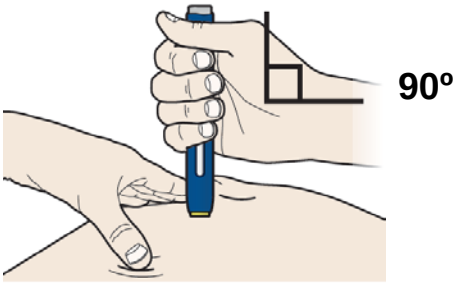


Pinch skin firmly between your thumb and fingers, creating an area about 2 inches (5 centimeters) wide.

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

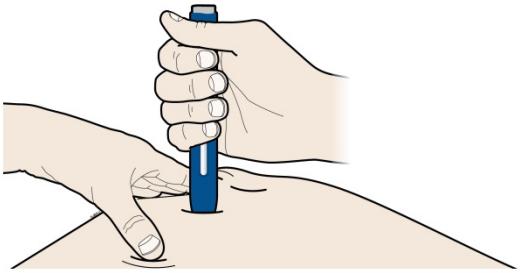
Step 3: Inject

A. Hold the stretch or pinch. With the orange cap off, PLACE autoinjector on skin at 90 degrees.



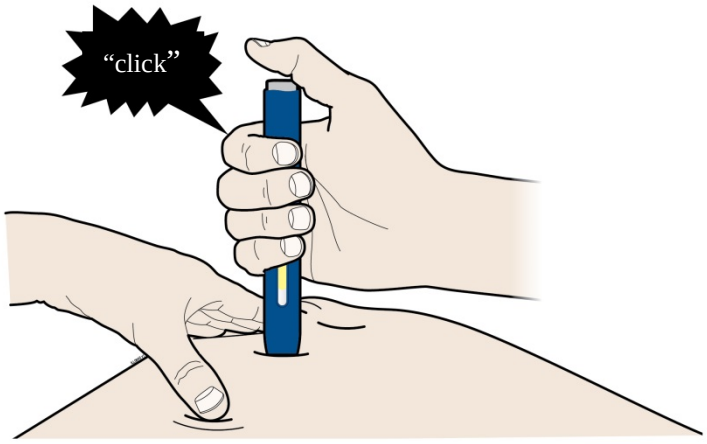
DO NOT touch the gray start button yet.

B. Firmly PUSH down autoinjector onto skin until it stops moving.

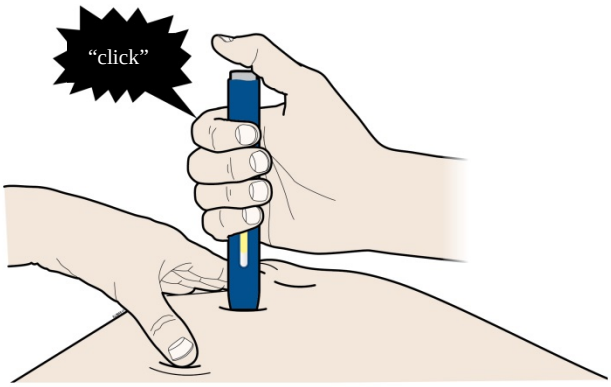


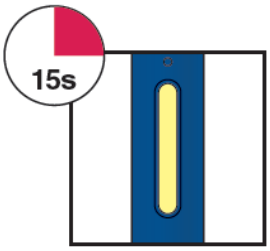
You must push all the way down but **DO NOT** touch the gray start button until you are ready to inject.

C. When you are ready to inject, PRESS the gray start button. You will hear a click.

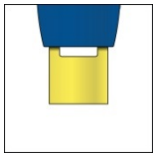


D. Keep PUSHING down on skin. Then LIFT thumb. Your injection could take about 15 seconds.





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
- recap the autoinjector or put fingers into the yellow safety guard
- 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 gray start button before I am ready to do the injection on my skin?

You can lift your finger up off the gray start button and place the prefilled autoinjector back on your injection site. Then, you can push the gray 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 gray start button. However, if you press the gray start button and the yellow safety guard is pushed into the autoinjector, the injection will begin.

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

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

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

The gray 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:

Hyperlipidemia

The usual dose for REPATHA is 140 mg every 2 weeks or 420 mg once monthly.

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 to 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 miss taking REPATHA: Please take REPATHA as soon as you can after the missed dose. Then, contact your doctor who will tell you when you should schedule your next doses.

What are possible side effects from using REPATHA:

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. These are not all the possible side effects you may feel when taking REPATHA. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

- Flu (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)
- Injection site reactions (redness, bruising, or pain)
- Rash
- Hives, red itchy bumps on your skin (urticarial)

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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 0701E
    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 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: September 10, 2015

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]REPATHA™
(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.

What is REPATHA used for?

REPATHA is used:

- along with diet and maximally tolerated statin therapy in adults with primary hyperlipidemia or who have clinical atherosclerotic cardiovascular disease, such as heart attacks or strokes, who need additional lowering of 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.

The effect of REPATHA on heart problems such as heart attacks, stroke, or death is not known.

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.

[†] Pre-filled syringes are not available in Canada

What are the ingredients in REPATHA?

The active substance is evolocumab.

- Each 1 mL prefilled syringe † contains 140 mg of evolocumab (140 mg/mL)
- Each 1 mL prefilled autoinjector 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 syringe †
- 140 mg/mL 1 mL single-use prefilled autoinjector (SureClick®)

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.

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

Pregnancy and Breast-feeding

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:

† Pre-filled syringes are not available in Canada

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

It is not known whether REPATHA is found in breast milk. It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking REPATHA, considering the benefit of breast-feeding 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 syringe [†]
- Single-use prefilled autoinjector (SureClick®)

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.

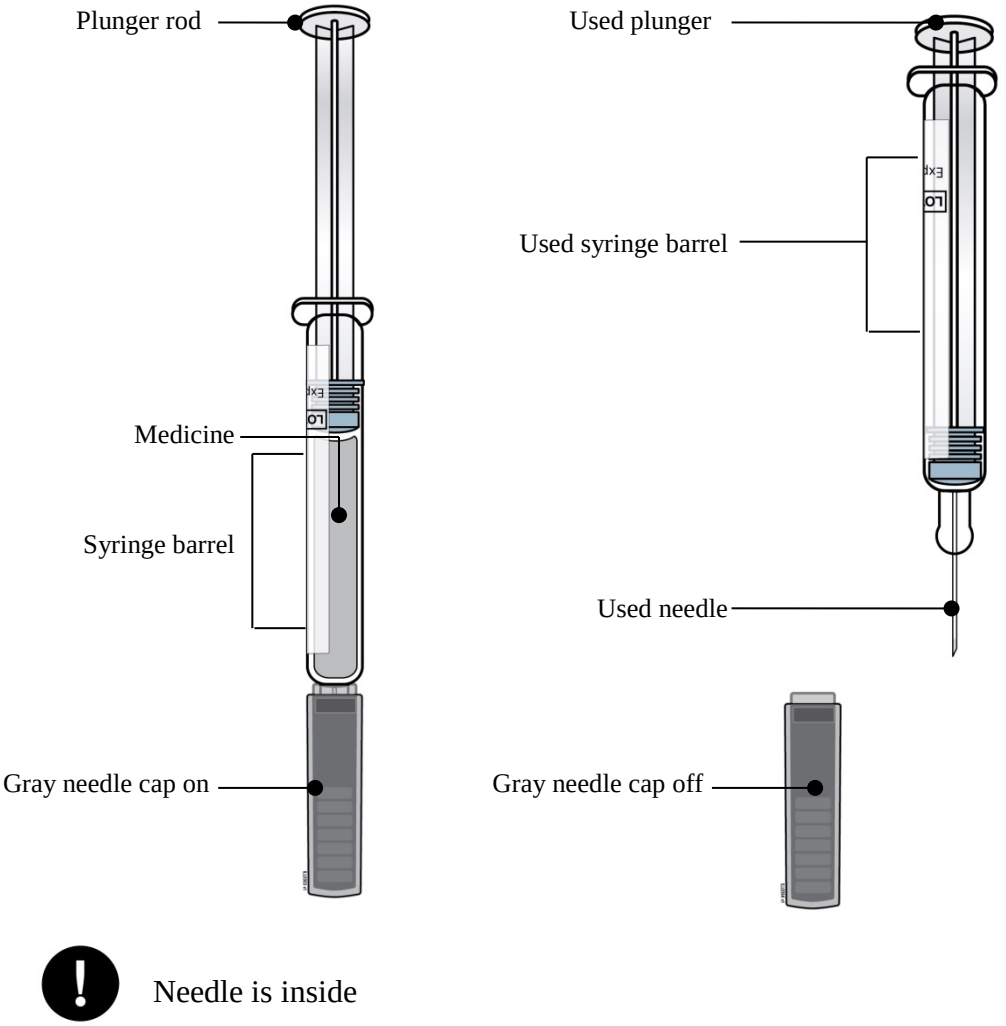
[†] Pre-filled syringes are not available in Canada

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.

† Pre-filled 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 gray 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 gray 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:

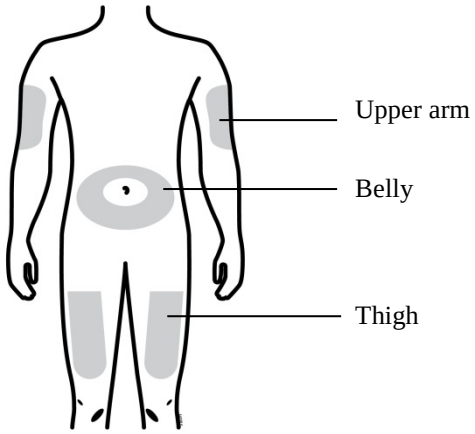
- One REPATHA prefilled syringe† in carton
- Alcohol wipes

† Pre-filled syringes are not available in Canada

- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container

✘ **DO NOT** use if expiration date on the REPATHA prefilled syringe† carton has passed.

C. Choose your injection site.

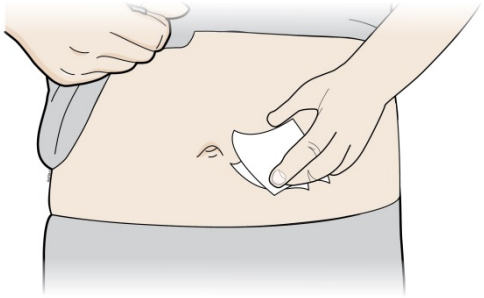


You can use:

- Thigh
- Belly, except for the 2 inches (5 centimeters) 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.

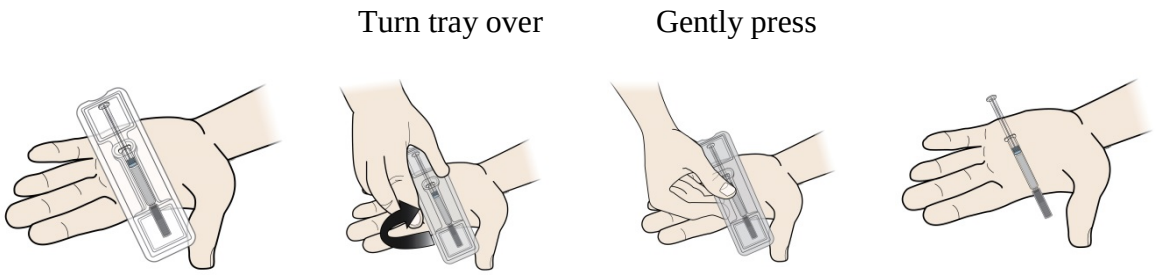


Clean your injection site with an alcohol wipe. Let your skin dry before injecting.

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

† Pre-filled syringes are not available in Canada

E. Remove prefilled syringe† from tray.



To remove:

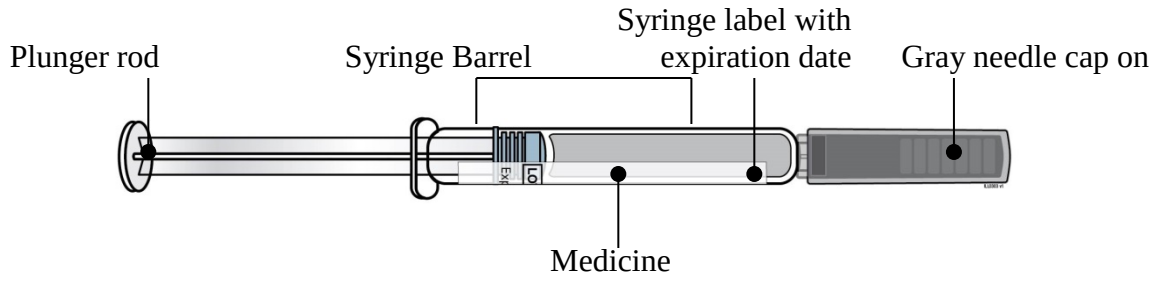
- Peel paper off of tray.
- Place the tray on your hand.
- Turn the tray over and gently press the middle of the tray's back to release the syringe into your palm.
- If prefilled syringe† does not release from tray, gently press on back of tray.

✘ **DO NOT**:

- Pick up or pull the prefilled syringe† by the plunger rod or gray needle cap. This could damage the syringe.
- Remove the gray 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.

Check that:

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

† Pre-filled syringes are not available in Canada

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

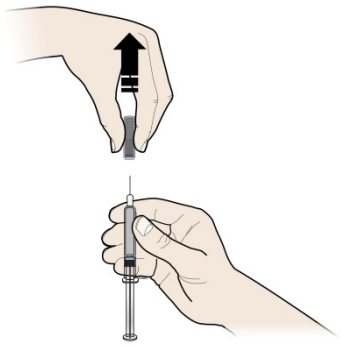
- any part of the prefilled syringe† appears cracked or broken.
- the gray needle cap is missing or not securely attached.
- the medicine is discolored or contains large lumps, flakes or colored particles.
- the expiration date on the prefilled syringe† has passed.

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 gray 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 gray needle cap. This can damage the needle.
- put the gray needle cap back onto the prefilled syringe†.

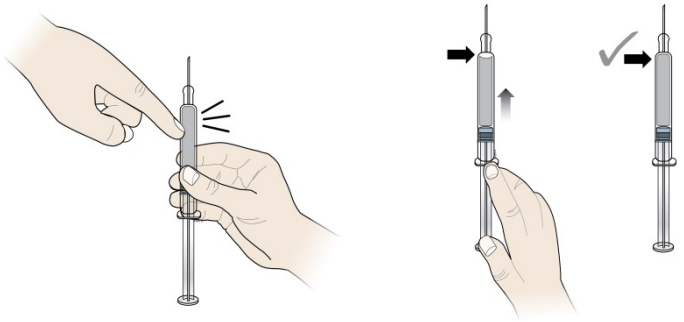
B. Remove the air bubble / gap.

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

If you notice an air bubble / gap:

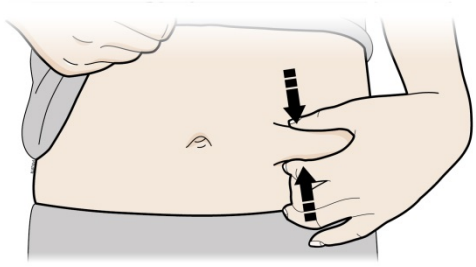
- Hold the prefilled syringe† with the needle facing up.
- Gently tap the syringe barrel with your fingers until the air bubble/gap rises to the top of the syringe.
- Slowly and gently push the plunger rod up to get the air out of the prefilled syringe†. Be very careful not to push out any medicine.

† Pre-filled syringes are not available in Canada



✘ **DO NOT** tap the syringe needle.

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

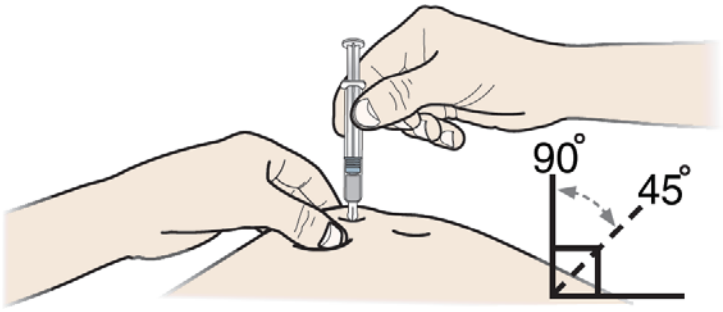


Pinch skin firmly between your thumb and fingers, creating an area about 5 centimeters wide.

It is important to keep the skin pinched while injecting.

Step 3: Inject

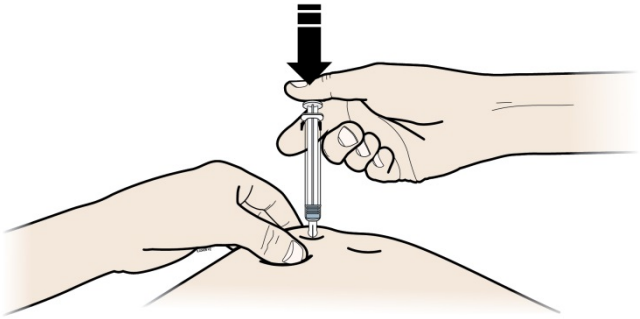
A. Hold the PINCH. Insert the needle into skin using a 45 to 90 degree angle.



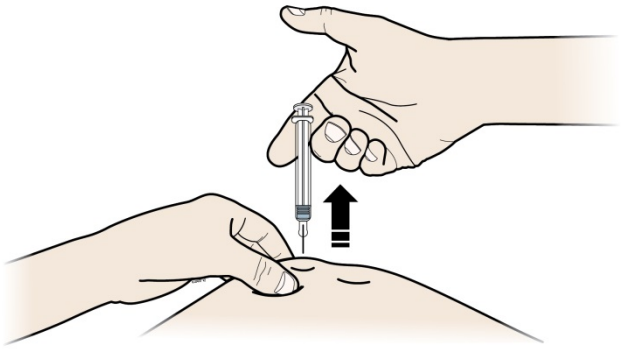
✘ **DO NOT** place your finger on the plunger rod while inserting the needle.

† Pre-filled 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.



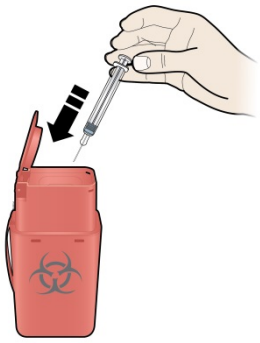
C. When done, RELEASE your thumb, and gently lift the syringe off skin.



✘ **DO NOT** put the gray 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

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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 to 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 miss taking REPATHA: Please take REPATHA as soon as you can after the missed dose. Then, contact your doctor who will tell you when you should schedule your next doses.

What are possible side effects from using REPATHA:

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. These are not all the possible side effects you may feel when taking REPATHA. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

- Flu (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)
- Injection site reactions (redness, bruising, or pain)
- Rash
- Hives, red itchy bumps on your skin (urticarial)

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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 0701E
    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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