

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125522Orig1s004

Trade Name: **Repatha injection**

Generic Name: **evolocumab**

Sponsor: **Amgen, Inc.**

Approval Date: **07/08/2016**

Indications: REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

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**CENTER FOR DRUG EVALUATION AND
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APPROVAL LETTER



BLA 125522/S-001, S-004

SUPPLEMENT APPROVAL

Amgen, Inc.
Attention: Adam Rupert
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 01320-1799

Dear Mr. Rupert:

Please refer to the following Supplemental Biologics License Applications (sBLAs) submitted under section 351(a) of the Public Health Service Act for Repatha (evolocumab) injection, 140 mg/mL:

1. Supplement -001 (S-001), dated and received September 10, 2015, proposes to market the Repatha Pushtronex system consisting of a Repatha (evolocumab) injection 420 mg/3.5 mL prefilled cartridge co-packaged with on-body infusion device, and associated labeling revisions.
2. Supplement -004 (S-004), dated and received February 29, 2016, submitted as a Changes Being Effected, as described under 21 CFR 601.12(f)(2), proposes to revise the Instructions for Use (IFU) for the approved SureClick® Autoinjector. Specifically, text and pictures have been added to convey that upon removal of the orange cap, the product should be injected within 5 minutes, and associated minor labeling revisions.

MANUFACTURING LOCATIONS

The final formulated prefilled cartridge drug product will be manufactured (b) (4)

DATING PERIOD

The dating period for the Repatha Pushtronex system shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of sterile filtration of the formulated drug product. The expiration date for the Repatha Pushtronex system shall not exceed the shortest shelf life of any of the Repatha Pushtronex system components.

Results of ongoing stability studies should be submitted to the annual report.

We have approved the stability protocols in your supplemental application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, and Instructions for Use [IFU]) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in these supplemental applications.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125522/S-001.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3105-1 Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the interim 1-year timepoint. These studies should use the methods equivalent to those used to evaluate device performance in the accelerated aging studies. The interim report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile (b) (4) Integrity Test, (b) (4) Function Test, and Adhesive Function Test.

The timetable you submitted on July 6, 2016, states that you will conduct this study according to the following schedule:

Interim Report (1-year timepoint) Submission: July 2017

- 3105-2 Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the interim 2-year and 31-day timepoint. These studies should use methods equivalent to those used to evaluate device performance in the accelerated aging studies. The final report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile (b) (4) Integrity Test, (b) (4) Function Test, and Adhesive Function Test.

The timetable you submitted on July 6, 2016, states that you will conduct this study according to the following schedule:

Interim Report (2-year and 31-day timepoint) Submission: July 2018

- 3105-3 Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the final 3-year and 31-day timepoint. These studies should use methods equivalent to those used to evaluate device performance in the accelerated aging studies. The final report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile (b) (4) Integrity Test, (b) (4) Function Test, and Adhesive Function Test.

The timetable you submitted on July 6, 2016, states that you will conduct this study according to the following schedule:

Interim Report (3-year and 31-day timepoint) Submission: July 2019

Submit clinical protocols to your IND 105188 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kati Johnson, Senior Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

James P. Smith, MD, MS
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Package Insert (S-001, S-004)

Patient Information (S-001)

Instructions for Use (S-001)

Instructions for Use (S-004)

Carton and Container Labeling (S-001)

Prefilled Cartridge Label

(b) (4) Lid Labeling

Carton (Trade)

Carton (Replacement)

Device Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
07/08/2016

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

Dosage and Administration (2.2) 7/2016

INDICATIONS AND USAGE

REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). (1.1)
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. (1.2)

Limitations of Use

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

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Allergic Reactions: Rash and urticaria have occurred. If signs or symptoms of serious allergic reactions occur, discontinue treatment with REPATHA, treat according to the standard of care, and monitor until signs and symptoms resolve. (5.1)

ADVERSE REACTIONS

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

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

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

Revised: 7/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Primary Hyperlipidemia

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

1.2 Homozygous Familial Hypercholesterolemia

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

1.3 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended subcutaneous dosage of REPATHA in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD is either 140 mg every 2 weeks OR 420 mg once monthly. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

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

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

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

2.2 Important Administration Instructions

- The 420 mg dose of REPATHA can be administered:
 - over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or
 - by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled syringe.
- Provide proper training to patients and/or caregivers on how to prepare and administer REPATHA prior to use, according to the Instructions for Use, including aseptic technique. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use REPATHA.
- Keep REPATHA in the refrigerator. Prior to use, allow REPATHA to warm to room temperature for at least 30 minutes for the single-use prefilled autoinjector or single-use prefilled syringe and for at least 45 minutes for the single-use on-body infusor with prefilled cartridge. Do not warm in any other

way. Alternatively, for patients and caregivers, REPATHA can be kept at room temperature at 68° F to 77°F (20°C to 25°C) in the original carton. However, under these conditions, REPATHA must be used within 30 days [*see How Supplied/Storage and Handling (16)*].

- Visually inspect REPATHA for particles and discoloration prior to administration. REPATHA is a clear to opalescent, colorless to pale yellow solution. Do not use if the solution is cloudy or discolored or contains particles.
- Administer REPATHA subcutaneously into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated using a single-use prefilled syringe, single-use prefilled autoinjector, or single-use on-body infusor with prefilled cartridge.
- Do not co-administer REPATHA with other injectable drugs at the same administration site.
- Rotate the site of each subcutaneous administration.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Adverse Reactions in Patients with Primary Hyperlipidemia and in Patients with Heterozygous Familial Hypercholesterolemia

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

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

Adverse Reactions in a 52-Week Controlled Trial

In a 52-week, double-blind, randomized, placebo-controlled trial (Study 2), 599 patients received 420 mg of REPATHA subcutaneously once monthly [see *Clinical Studies (14.1)*]. The mean age was 56 years (range: 22 to 75 years), 23% were older than 65 years, 52% women, 80% White, 8% Black, 6% Asian, and 6% Hispanic. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients in Study 2, are shown in Table 1. Adverse reactions led to discontinuation of treatment in 2.2% of REPATHA-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to REPATHA treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for REPATHA and placebo, respectively).

Table 1. Adverse Reactions Occurring in Greater than or Equal to 3% of REPATHA-treated Patients and More Frequently than with Placebo in Study 2

	Placebo (N = 302) %	REPATHA (N = 599) %
Nasopharyngitis	9.6	10.5
Upper respiratory tract infection	6.3	9.3
Influenza	6.3	7.5
Back pain	5.6	6.2
Injection site reactions [†]	5.0	5.7
Cough	3.6	4.5
Urinary tract infection	3.6	4.5
Sinusitis	3.0	4.2
Headache	3.6	4.0
Myalgia	3.0	4.0
Dizziness	2.6	3.7
Musculoskeletal pain	3.0	3.3
Hypertension	2.3	3.2
Diarrhea	2.6	3.0
Gastroenteritis	2.0	3.0

[†]includes erythema, pain, bruising

Adverse Reactions in Seven Pooled 12-Week Controlled Trials

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

at least 1% of REPATHA-treated patients, and more frequently than in placebo-treated patients, are shown in Table 2.

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

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

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

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

The adverse reactions described below are from a pool of the 52-week trial (Study 2) and seven 12-week trials. The mean and median exposure durations of REPATHA in this pool of eight trials were 20 weeks and 12 weeks, respectively.

Local Injection Site Reactions

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

Allergic Reactions

Allergic reactions occurred in 5.1% and 4.7% of REPATHA-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for REPATHA and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).

Neurocognitive Events

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

Low LDL-C Levels

In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1988 patients treated with REPATHA had at least one LDL-C value < 25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and REPATHA dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C

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

Musculoskeletal Events

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

Adverse Reactions in Patients with Homozygous Familial Hypercholesterolemia

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

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

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of REPATHA has been evaluated using an electrochemiluminescent bridging screening immunoassay for the detection of binding anti-drug antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In a pool of placebo- and active-controlled clinical trials, 0.1% of patients treated with at least one dose of REPATHA tested positive for binding antibody development. Patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies; none of the patients tested positive for neutralizing antibodies.

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

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to REPATHA with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data available on use of REPATHA in pregnant women to inform a drug-associated risk. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

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

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

8.5 Geriatric Use

In controlled studies, 1420 patients treated with REPATHA were ≥ 65 years old and 171 were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is needed in patients with mild to moderate renal impairment. No data are available in patients with severe renal impairment [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

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

11 DESCRIPTION

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Evolocumab exhibits non-linear kinetics as a result of binding to PCSK9. Administration of the 140 mg dose in healthy volunteers resulted in a C_{max} mean (standard deviation [SD]) of 18.6 (7.3) $\mu\text{g/mL}$ and AUC_{last} mean (SD) of 188 (98.6) $\text{day}\cdot\mu\text{g/mL}$. Administration of the 420 mg dose in healthy volunteers resulted in a C_{max} mean (SD) of 59.0 (17.2) $\mu\text{g/mL}$ and AUC_{last} mean (SD) of 924 (346) $\text{day}\cdot\mu\text{g/mL}$. Following a single 420 mg intravenous dose, the mean (SD) systemic clearance was estimated to be 12 (2) mL/hr . An approximate 2- to 3-fold accumulation was observed in trough serum concentrations (C_{min} [SD] 7.21 [6.6]) following 140 mg doses administered subcutaneously every 2 weeks or following 420 mg doses administered subcutaneously monthly (C_{min} [SD] 11.2 [10.8]), and serum trough concentrations approached steady state by 12 weeks of dosing.

Absorption

Following a single subcutaneous dose of 140 mg or 420 mg evolocumab administered to healthy adults, median peak serum concentrations were attained in 3 to 4 days, and estimated absolute bioavailability was 72%.

Distribution

Following a single 420 mg intravenous dose, the mean (SD) steady-state volume of distribution was estimated to be 3.3 (0.5) L.

Metabolism and Elimination

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

Specific Populations

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

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

Renal Impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of evolocumab. Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) have not been studied.

Hepatic Impairment

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

Pregnancy

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

Drug Interaction Studies

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease

Study 1 was a multicenter, double-blind, randomized controlled trial in which patients were initially randomized to an open-label specific statin regimen for a 4-week lipid stabilization period followed by random assignment to subcutaneous injections of REPATHA 140 mg every 2 weeks, REPATHA 420 mg once monthly, or placebo for 12 weeks. The trial included 296 patients with atherosclerotic CVD who received REPATHA or placebo as add-on therapy to daily doses of atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg. Among these patients, the mean age at baseline was 63 years (range: 32 to 80 years), 45% were ≥ 65 years old, 33% women, 98% White, 2% were Black, < 1% Asian and 5% Hispanic or Latino. After 4 weeks of statin therapy, the mean baseline LDL-C was 108 mg/dL.

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

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

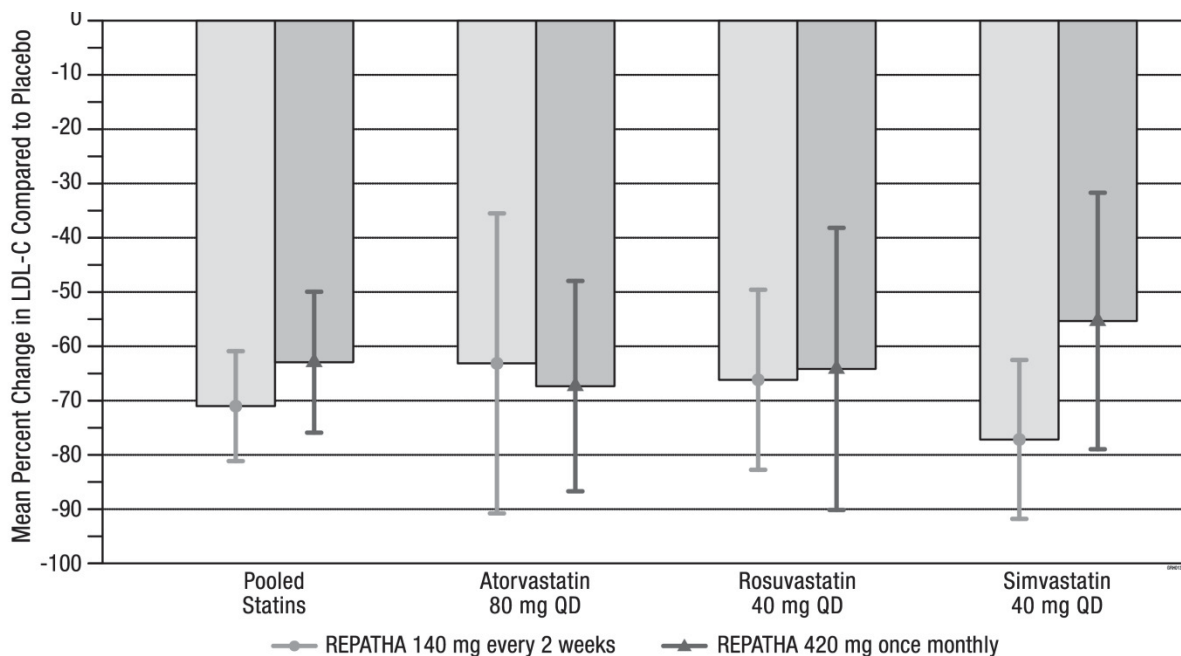
Table 3. Effect of REPATHA on Lipid Parameters in Patients with Atherosclerotic CVD on Atorvastatin 80 mg, Rosuvastatin 40 mg, or Simvastatin 40 mg (Mean % Change from Baseline to Week 12 in Study 1)

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

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

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

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



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

Error bars indicate 95% confidence intervals

Study 2 was a multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 139 patients with atherosclerotic CVD who received protocol-determined background lipid-lowering therapy of atorvastatin 80 mg daily with or without ezetimibe 10 mg daily. After stabilization on

background therapy, patients were randomly assigned to the addition of placebo or REPATHA 420 mg administered subcutaneously once monthly. Among these patients, the mean age at baseline was 59 years (range: 35 to 75 years), 25% were ≥ 65 years, 40% women, 80% White, 3% Black, 5% Asian, and $< 1\%$ Hispanic or Latino. After stabilization on the assigned background therapy, the mean baseline LDL-C was 105 mg/dL.

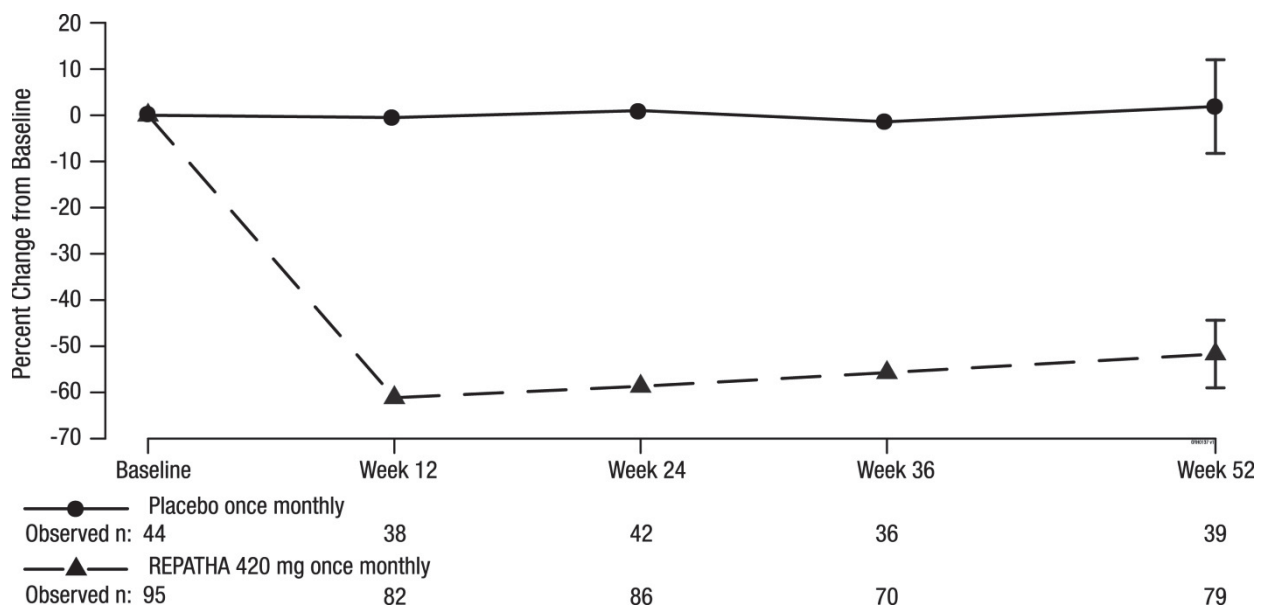
In these patients with atherosclerotic CVD on maximum-dose atorvastatin therapy with or without ezetimibe, the difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -54 % (95% CI: -65%, -42%; $p < 0.0001$) (Table 4 and Figure 2). For additional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

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

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

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

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



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

14.2 Heterozygous Familial Hypercholesterolemia (HeFH)

Study 3 was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 329 patients with heterozygous familial hypercholesterolemia (HeFH) on statins with or without other lipid-lowering

therapies. Patients were randomized to receive subcutaneous injections of REPATHA 140 mg every two weeks, 420 mg once monthly, or placebo. HeFH was diagnosed by the Simon Broome criteria (1991). In Study 3, 38% of patients had clinical atherosclerotic cardiovascular disease. The mean age at baseline was 51 years (range: 19 to 79 years), 15% of the patients were ≥ 65 years old, 42% were women, 90% were White, 5% were Asian, and 1% were Black. The average LDL-C at baseline was 156 mg/dL with 76% of the patients on high-intensity statin therapy.

In these patients with HeFH on statins with or without other lipid lowering therapies, the differences between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -61% (95% CI: -67%, -55%; $p < 0.0001$) and -60% (95% CI: -68%, -52%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 5.

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

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

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

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

14.3 Homozygous Familial Hypercholesterolemia (HoFH)

Study 4 was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with homozygous familial hypercholesterolemia (HoFH). In this trial, 33 patients received subcutaneous injections of 420 mg of REPATHA once monthly and 16 patients received placebo as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe). The mean age at baseline was 31 years, 49% were women, 90% White, 4% were Asian, and 6% other. The trial included 10 adolescents (ages 13 to 17 years), 7 of whom received REPATHA. The mean LDL-C at baseline was 349 mg/dL with all patients on statins (atorvastatin or rosuvastatin) and 92% on ezetimibe. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents.

In these patients with HoFH, the difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -31% (95% CI: -44%, -18%; $p < 0.0001$). For additional results see Table 6.

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

Pharmacy

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

For Patients/Caregivers

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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



REPATHA[®] (evolocumab)

Manufactured by:

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

U.S. License Number 1080

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

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Patient Information
REPATHA® (ri-PAth-a)
(evolocumab)
Injection, for Subcutaneous Use

What is REPATHA?

REPATHA is an injectable prescription medicine called a PCSK9 inhibitor. REPATHA is used:

- along with diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (an inherited condition that causes high levels of LDL) or atherosclerotic heart or blood vessel problems, who need additional lowering of LDL cholesterol.
- along with diet and other LDL lowering therapies in people with homozygous familial hypercholesterolemia (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 13 years of age or in children who do not have HoFH.

Who should not use REPATHA?

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

What should I tell my healthcare provider before using REPATHA?

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

- are allergic to rubber or latex. The needle covers on the single-use prefilled syringes and within the needle caps on the single-use prefilled SureClick® autoinjectors contain dry natural rubber. The single-use Pushtronex™ system (on-body infusor with prefilled cartridge) is not made with natural rubber latex.
- are pregnant or plan to become pregnant. It is not known if REPATHA will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking REPATHA.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take REPATHA or breastfeed. You should not do both without talking to your healthcare provider first.

Tell your healthcare provider or pharmacist about any prescription and over-the-counter medicines you are taking or plan to take, including natural or herbal remedies.

How should I use REPATHA?

- **See the detailed “Instructions for Use” that comes with this patient information about the right way to prepare and administer REPATHA.**
- Use REPATHA exactly as your healthcare provider tells you to use it.
- REPATHA is administered under the skin (subcutaneously), every 2 weeks or 1 time each month.
- REPATHA comes as a single-use (1 time) prefilled autoinjector (SureClick® autoinjector), as a single-use prefilled syringe or as a single-use Pushtronex™ system (on-body infusor with prefilled cartridge). Your healthcare provider will prescribe the type and dose that is best for you.
- If your healthcare provider prescribes you the monthly dose, you may use:
 - a single-use on-body infusor with prefilled cartridge over 9 minutes, or
 - 3 separate injections in a row, using a different single-use prefilled syringe or single-use prefilled autoinjector for each injection. Give all of these injections within 30 minutes.
- If your healthcare provider decides that you or a caregiver can administer REPATHA, you or your caregiver should receive training on the right way to prepare and administer REPATHA. **Do not** try to administer REPATHA until you have been shown the right way by your healthcare provider or nurse.
- **Do not** administer REPATHA together with other injectable medicines at the same injection site.
- Always check the label of your single-use prefilled autoinjector, single-use prefilled syringe, or single-use on-body infusor with prefilled cartridge to make sure you have the correct medicine and the correct dose of REPATHA before each administration.
- If you forget to use 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 the 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.
- If you use more REPATHA than you should, talk to your healthcare provider or pharmacist.
- **Do not** stop using REPATHA without talking with your healthcare provider. If you stop using REPATHA, your cholesterol levels can increase.

What are possible side effects of REPATHA?

REPATHA can cause side effects including:

- **allergic reactions.** 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 most common side effects of REPATHA include: runny nose, sore throat, symptoms of the common cold, flu or flu-like symptoms, back pain, and redness, pain, or bruising at the injection site.

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

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

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

General information about the safe and effective use of REPATHA.

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

This Patient Information leaflet summarizes the most important information about REPATHA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about REPATHA that is written for healthcare professionals.

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

What are the ingredients in REPATHA?

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

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

U.S. License Number 1080

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

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

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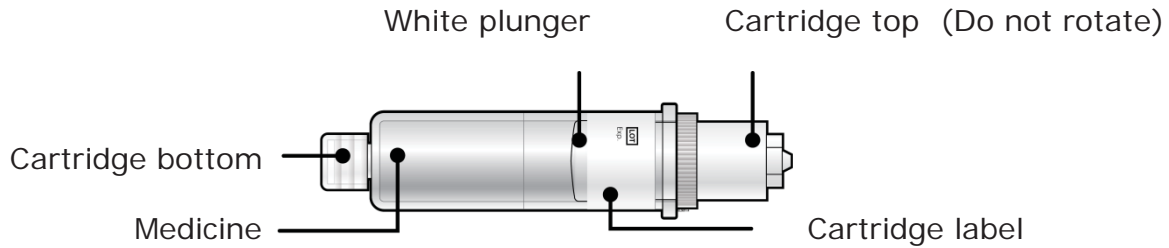
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Instructions for use:
Pushtronex™ System for
Repatha® (ri-PAth-a)
(evolocumab)

Single-Use On-Body Infusor and Prefilled Cartridge

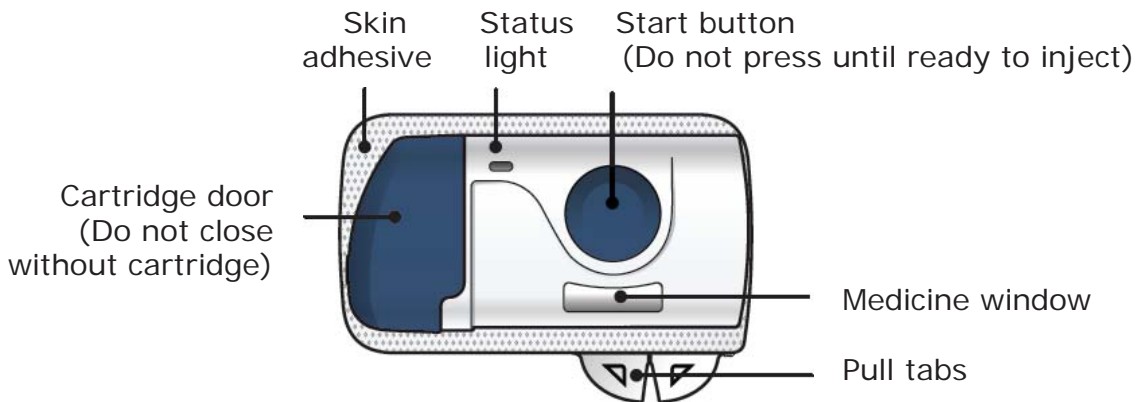
Guide to parts

Prefilled Cartridge

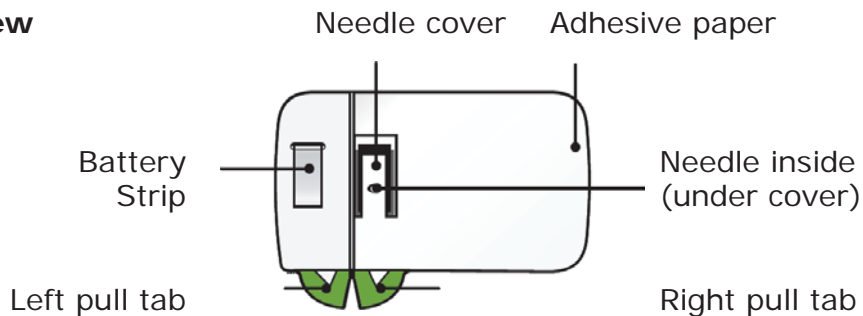


On-Body Infusor

Front view



Back view



Important: Needle is inside.

Important

Before you use the on-body infusor and prefilled cartridge for use with Repatha (evolocumab), read this important information:

- It is important that you do not try to give yourself the injection unless you have received training from your healthcare provider.

Storing your on-body infusor and prefilled cartridge

- Keep the on-body infusor and prefilled cartridge in the original carton to protect from light or physical damage.
- The on-body infusor and prefilled cartridge must be kept in the refrigerator 36 °F to 46 °F (2 °C to 8 °C).
- If removed from the refrigerator, the on-body infusor should be kept at room temperature at 68° F to 77°F (20° C to 25°C) in the original carton and must be used within 30 days.
- **Do not** store the on-body infusor and prefilled cartridge in temperatures above 77°F (25°C) such as in your vehicle's glove box or trunk. **Do not** freeze.

Using your on-body infusor and prefilled cartridge

- **Do not** shake the on-body infusor or prefilled cartridge.
- **Do not** remove the on-body infusor and prefilled cartridge from the box or clear tray until you are ready to inject.
- **Do not** touch the start button until you place the loaded on-body infusor and prefilled cartridge onto your skin and are ready to inject.
- You can only press the start button 1 time. If an error occurs, the on-body infusor cannot be used.
- **Do not** use the on-body infusor and prefilled cartridge if either has been dropped onto a hard surface. Part of the on-body infusor and prefilled cartridge may be broken even if you cannot see the break. Use a new on-body infusor and prefilled cartridge.
- **Do not** reuse the on-body infusor and prefilled cartridge. The on-body infusor and prefilled cartridge are for single use only.
- **Do not** let the on-body infusor get wet from water or any other liquids. It contains electronics that should not get wet.
- The single use on-body infusor for subcutaneous injection is made to only be used with the prefilled cartridge.
- Moderate physical activities can be done during the injection process, such as walking, reaching and bending.
- **Do not** use the on-body infusor and prefilled cartridge after the expiration date on the carton.
- The on-body infusor and prefilled cartridge are not made with natural rubber latex.

A healthcare provider who knows how to use the on-body infusor should be able to answer your questions. For more information, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

Keep the on-body infusor and prefilled cartridge out of the reach of children.

Step 1: Prepare

- 1A** Remove the on-body infusor and prefilled cartridge carton from the refrigerator. Wait 45 minutes.

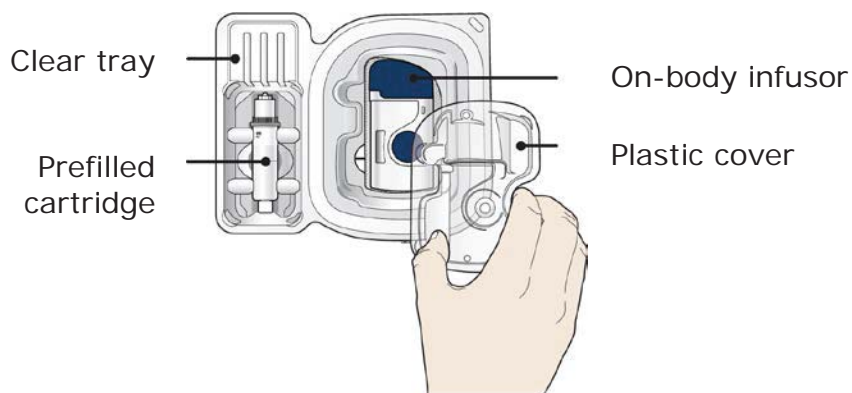


Important: Wait at least 45 minutes for the on-body infusor and prefilled cartridge to naturally reach room temperature in the carton.

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

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

- 1B** Open the carton and peel away the white paper cover. Remove the plastic cover from the clear tray.



Leave the on-body infusor and prefilled cartridge in the clear tray until you are ready to inject.

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

- 1C** Gather all materials needed for your injection and then wash your hands well with soap and water.

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

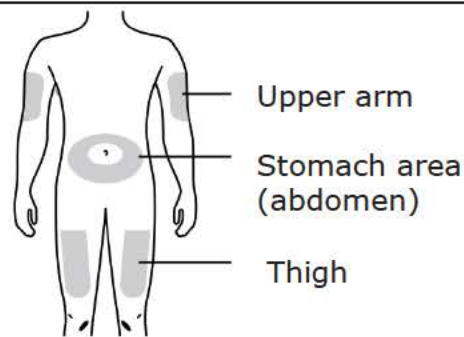
- Clear tray containing the on-body infusor and prefilled cartridge
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



- 1D** To securely attach the on-body infusor, 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:

- Your thigh
- Stomach area (abdomen), except for a **two**-inch area right around your navel
- Outer area of upper arm (only if someone else is giving the injection)



Clean your 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, scars, stretch marks, moles and excessive hair.

Important: To attach the on-body infusor securely, it is important to use a firm and flat skin surface.

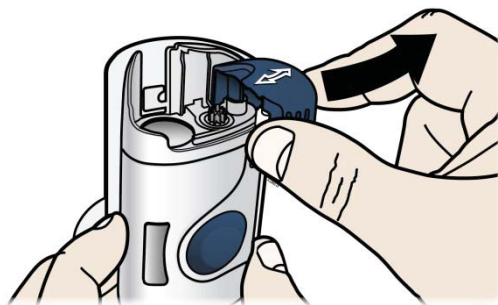
Step 2: Get ready

- 2A** Open the on-body infusor by swinging the cartridge door to the right. Then, **leave the door open**. **Do not** close the cartridge door before the cartridge is loaded.

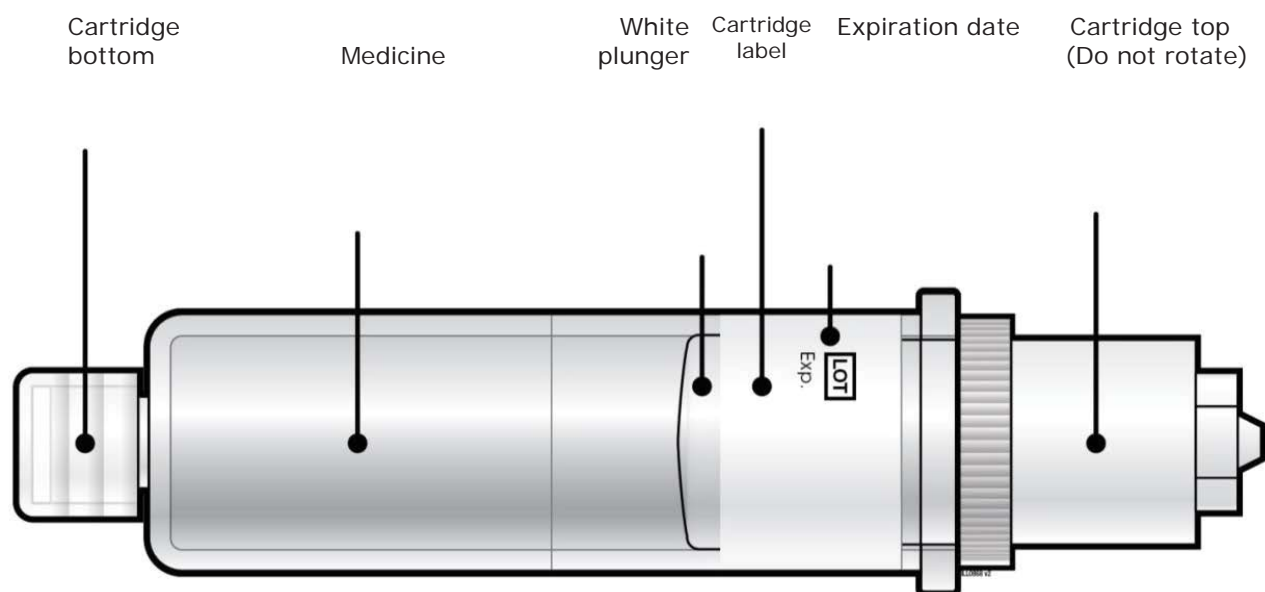
If you accidentally close the cartridge door, press on the left side of the door to release the door latch.

If you are still unable to open the door, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

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



- 2B** Inspect the cartridge.



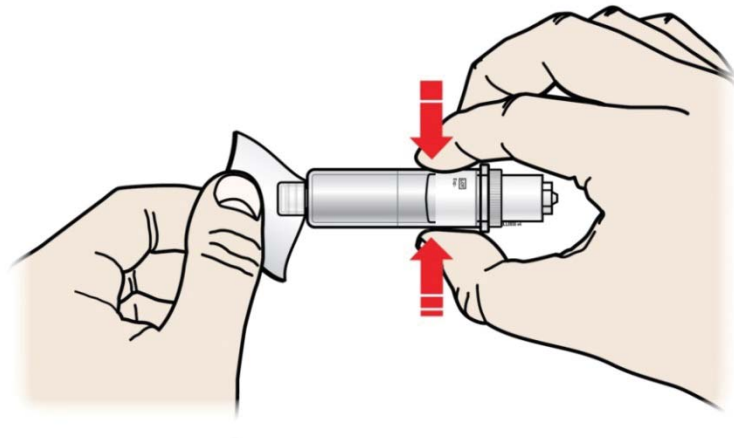
Check the expiration date: **do not** use if this date has passed.

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

- **Do not** use if the medicine is cloudy or discolored or contains flakes or particles.
- **Do not** use if any part of the cartridge looks cracked or broken.
- **Do not** use if pieces of the cartridge are missing or not securely attached.

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

2C Clean the cartridge bottom.

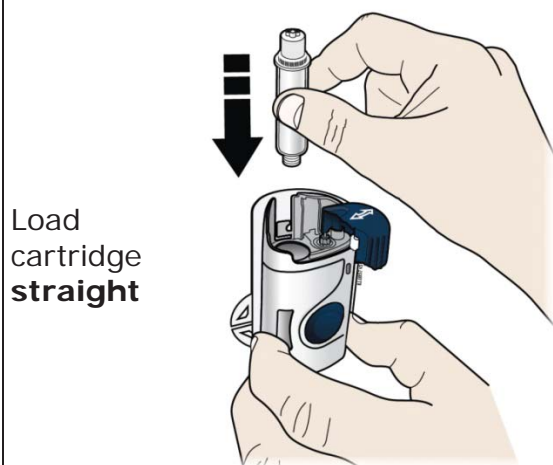


Grab Here

With 1 hand, hold the cartridge barrel and clean the cartridge bottom with an alcohol wipe.

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

2D Load the cleaned cartridge into the on-body infusor and firmly press on the top until it is secured in place.



Insert the cartridge bottom first.

- **Do not** touch the start button until you have placed the loaded on-body infusor on your skin.

2E	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.
-----------	--

Squeeze
Tight



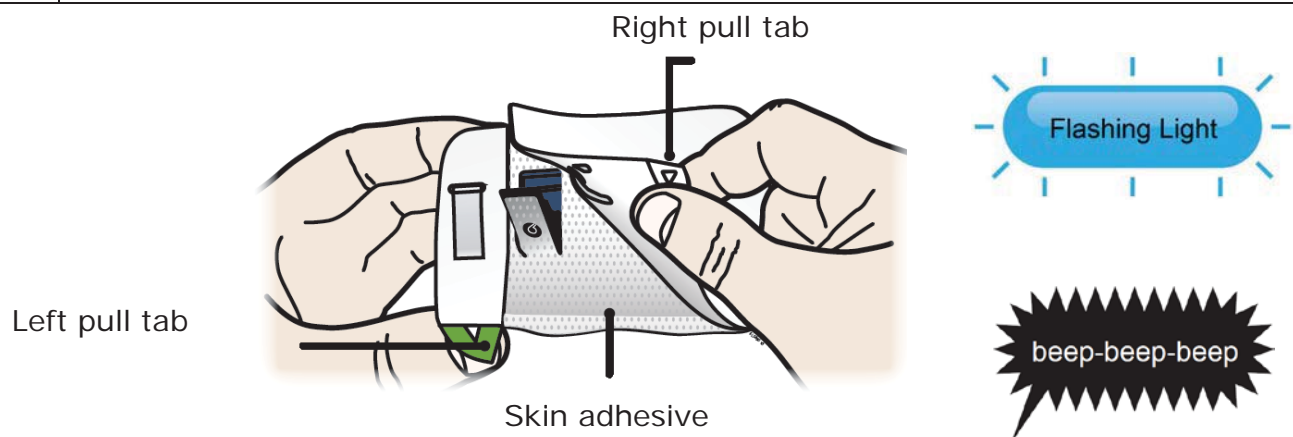
Make sure the cartridge fits securely in the on-body infusor before you close the door.

- **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 on-body infusor on your skin.

Important: After you load the on-body infusor, go to the next step right away.

Step 3: Inject

3A	Peel away both green pull tabs to show the adhesive. The on-body infusor is on when the blue status light flashes.
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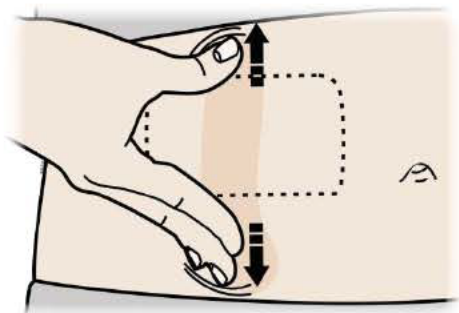
You must remove **both** green pull tabs to turn the loaded on-body infusor on. You will

hear beeping and see a flashing blue status light.

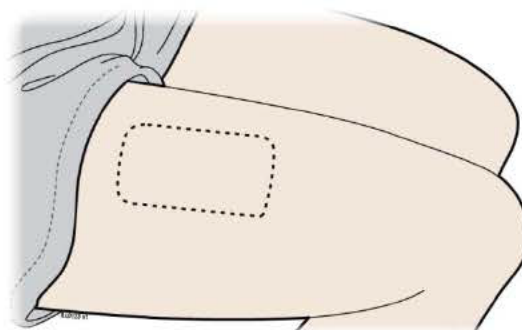
- **Do not** pull the skin adhesive backing off of the On-Body Infusor.
- **Do not** touch the skin adhesive.
- **Do not** touch the start button until you have placed the loaded on-body infusor on your skin.
- **Do not** touch the needle cover area.
- **Do not** place the loaded on-body infusor on your body if the red status light flashes continuously.
- **Do not** fold the skin adhesive over onto itself.

3B Choose your on-body infusor injection site. Only use the outer arm if someone else is giving the injection.

Stomach area placement



Thigh placement



or

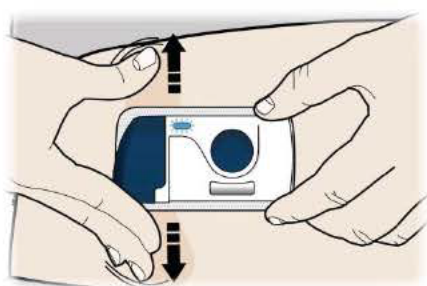
Stretch method for stomach

Do not stretch for thigh

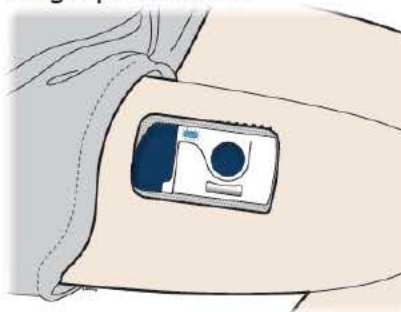
Important: Adjust your body posture to avoid skin folds and bulges.

3C When the blue light flashes, the on-body infusor is ready. Keep the stretch (stomach area method only). Hold the loaded on-body infusor with the blue light visible, and place it on your skin. You may hear beeps.

Stomach area placement



Thigh placement



or

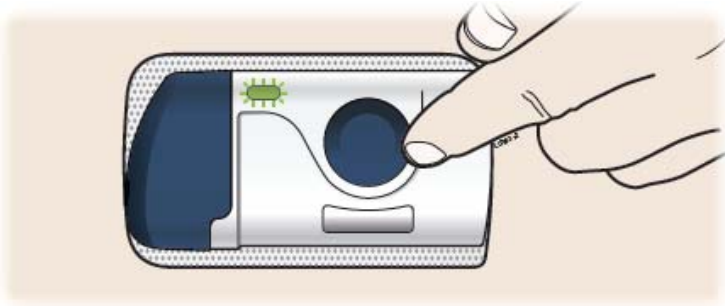


The loaded on-body infusor will lay flat on your body. Make sure all of the adhesive is attached to your skin. Run a finger around the adhesive edges to secure it.

Make sure clothing does not get in the way of the loaded on-body infusor, and you can see the blue light at all times.

- **Do not** move the loaded on-body infusor after it has been placed onto your skin.

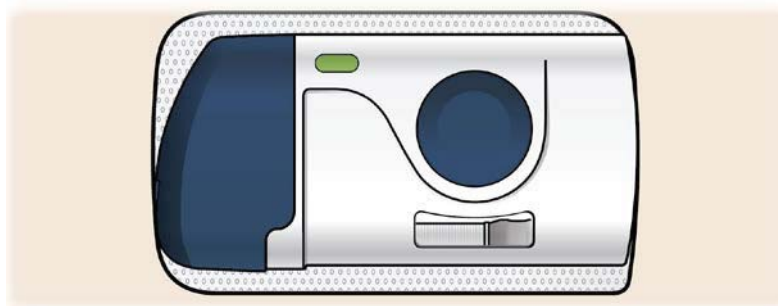
3D Firmly **press and release** the start button. A flashing green light and a click signals the injection has started.



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

Important: If medication leaks from the on-body infusor, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

3E The 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.

Solid Light

Injection is finished when:

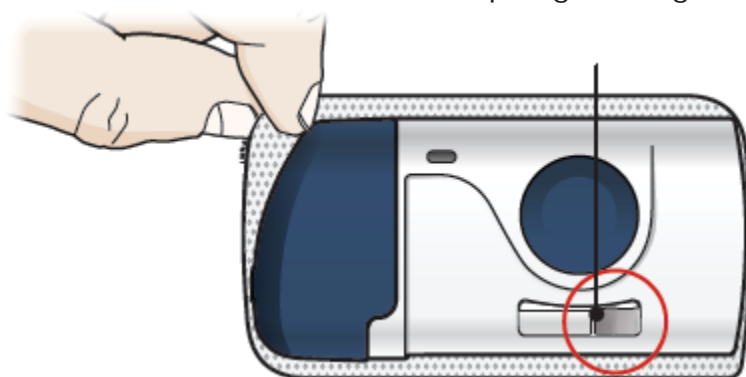
- The status light changes to **solid green**.
- You hear several beeps.
- The plunger fills medicine window all the way.

beep-beep-beep

Step 4: Finish

- 4A** When the injection is done, grab the skin adhesive to carefully peel the on-body infusor off skin. After removal, check the medicine window. The green light should now be off.

Used plunger filling medicine window



Light Off

beep-beep-beep

Check to see that the used plunger fills the medicine window all the way, and the green solid light turns off, letting you know all medicine has been injected. If the plunger did not fill the window, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

- The used on-body infusor 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 on-body infusor.

4B Throw away the used on-body infusor in a sharps container.

- The on-body infusor contains batteries, electronics, and a needle.
- Put the used on-body infusor in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the on-body infusor in your household trash.
- If you do not have a FDA-cleared 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 state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.



Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- **Do not** recycle the on-body infusor or sharps disposal container or throw them into household trash.

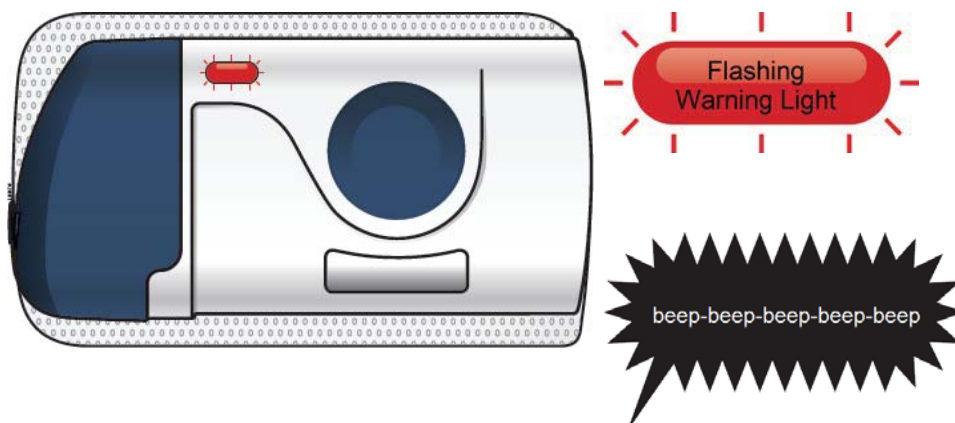
Important: Always keep the sharps disposal container out of the reach of children.

4C Check 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.

Troubleshooting

What do I do if the loaded on-body infusor status light continuously flashes red and you hear beeps?



Stop using the loaded on-body infusor. If the on-body infusor is attached to your body, carefully remove it. Call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

Commonly Asked Questions

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

This means that an error has happened. When this happens, the injection will stop by itself. Remove the on-body infusor from your body by slowly and carefully peeling it off of your skin, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What should I do if the on-body infusor comes off my body during the injection?

Though unlikely, if the on-body infusor comes off during the injection, the on-body infusor will make a beeping sound, you will see the blinking red light, and the on-body infusor will stop. The loaded on-body infusor can no longer be used, and do not reapply to your body. Call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What if I push the start button before I place the on-body infusor on my skin?

If you have removed the adhesive backing and pressed the start button, the on-body infusor will make a beeping sound and you will see the blinking red light. The on-body infusor will stop. Stop using the on-body infusor, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What if the on-body infusor 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 on-body infusor, including the adhesive paper over the battery strip and needle cover. If both green pull tabs have been fully removed and the on-body infusor still does not turn on, use a new on-body infusor and prefilled cartridge. Call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What if I push the start button and nothing happens?

Remove the on-body infusor by slowly and carefully peeling it away from your skin.

Do not reapply the same on-body infusor that you have already placed on your skin.
Call 1-844-REPATHA (1-844-737-2842) or visit [www. REPATHA.com](http://www.REPATHA.com)

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

To open the On-Body Infusor door, press on the left side of the door to release the door latch. If you are still unable to open the door, call 1-844-REPATHA (1-844-737-2842) or visit www. REPATHA.com

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



Manufactured by:
Amgen Inc.
Thousand Oaks, CA 91320-1799
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<part number> Revised: XX/XXXX vX

U.S. License Number 1080

Additional environmental conditions

Relative humidity range is 15% to 85%.

Altitude range is -984 feet to 11483 feet (-300 meters to 3500 meters).






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






Warning: Do not modify the device.

On-body infusor operating temperature range is 59°F to 104°F (15°C to 40°C).

www.devicepatents.com

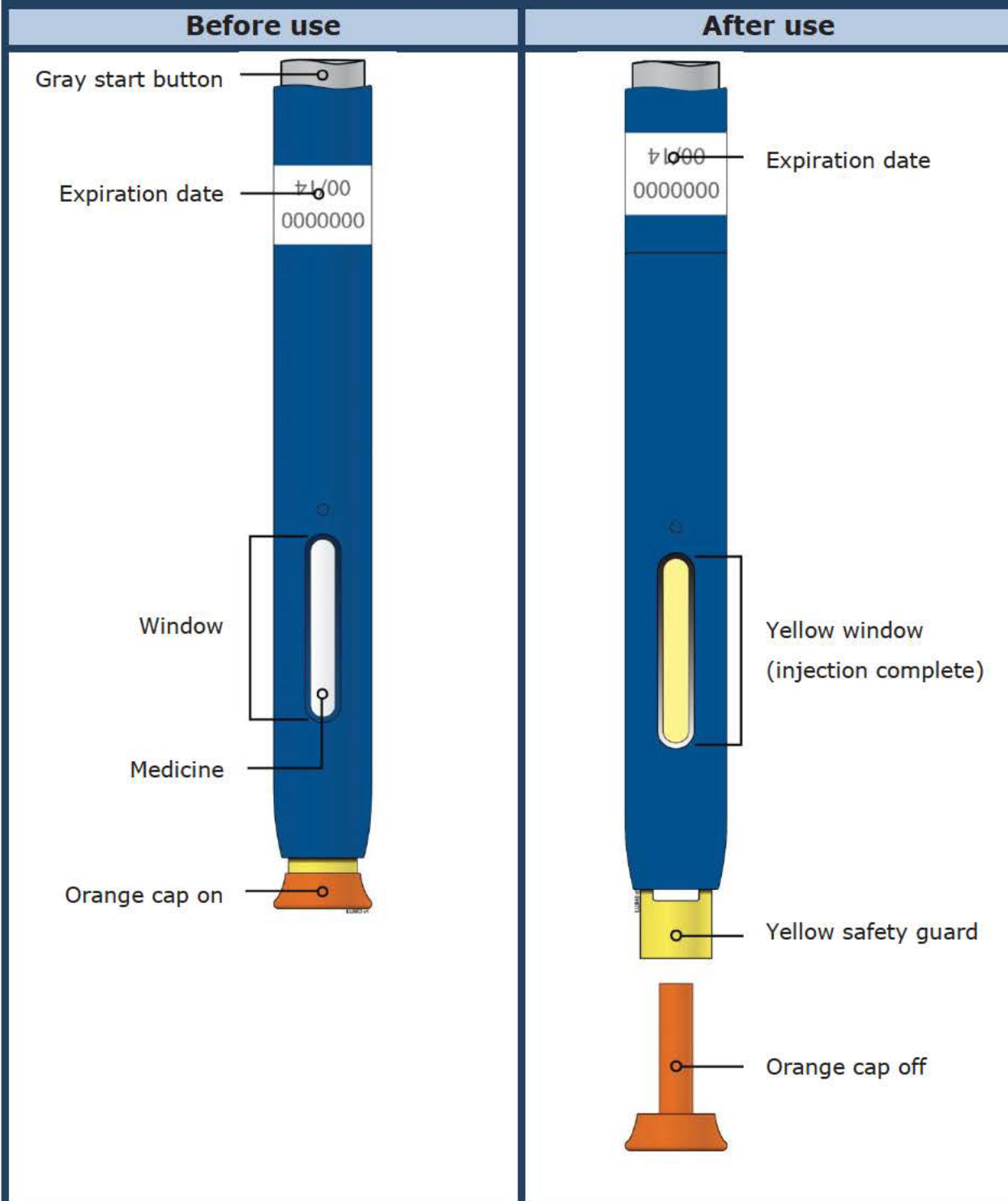
SYMBOL TABLE

				
Do not re-use	Serial number	Type BF Applied Part	Do not use if packaging is	On-Body Infusor

			damaged	containing 420 mg/3.5 mL (120 mg/mL)
 <p>Sterilized using ethylene oxide</p>	 <p>Refer to Instructions for Use</p>	 <p>Lot number</p>	 <p>Keep dry</p>	 <p>Open here</p>

Instructions for Use
Repatha® (ri-Path-a)
(evolocumab)
Single-Use Prefilled SureClick® Autoinjector

Guide to parts



Important: Needle is inside

Important

Before you use a Single-Use Repatha SureClick autoinjector, read this important information:

- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.
- The orange cap on the Repatha SureClick autoinjector contains a needle cover (located inside the cap) that contains dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.

Storage of Repatha:

- Keep the Repatha SureClick autoinjector in the original carton to protect from light during storage.
- Keep the Repatha SureClick autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If removed from the refrigerator, the Repatha SureClick autoinjector should be kept at room temperature at 68°F to 77°F (20°C to 25°C) in the original carton and must be used within **30** days.
- **Do not** freeze the Repatha SureClick autoinjector or use a Repatha SureClick autoinjector that has been frozen.

Using Repatha:

- **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, and call 1-844-REPATHA (1-844-737-2842).
- **Do not** use the Repatha SureClick autoinjector after the expiration date.

A healthcare provider who knows how to use the Repatha SureClick autoinjector should be able to answer your questions. For more information, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

Keep the Repatha SureClick autoinjector out of the sight and reach of children.

Step 1: Prepare

1A Remove 1 Repatha SureClick autoinjector from the package.

Carefully lift the autoinjector straight up out of the box.

Put the original package with any unused autoinjectors back in the refrigerator.

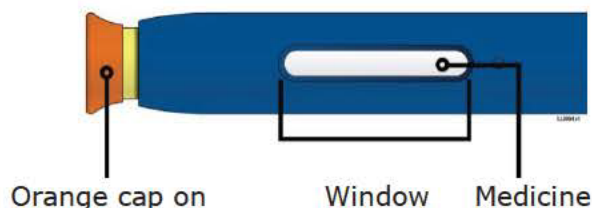
Wait at least **30 minutes** for the autoinjector to reach room temperature before injecting.



This is important for administering the entire dose and helps minimize discomfort. Repatha may take longer to inject if it has not reached room temperature. **Do not** heat the autoinjector. Let it warm up on its own.

- **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

1B Inspect the Repatha SureClick autoinjector.



Check the expiration date. **Do not** use the Repatha SureClick autoinjector past the expiration date printed on the label.

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

- **Do not** use the autoinjector if the medicine is cloudy or discolored or contains particles.
- **Do not** use the autoinjector if any part appears cracked or broken.
- **Do not** use the autoinjector if the autoinjector has been dropped.
- **Do not** use the autoinjector if the orange cap is missing or not securely attached.

In all cases, use a new autoinjector, and call 1-844-REPATHA (1-844-737-2842).

1C Gather all materials needed for your injection.

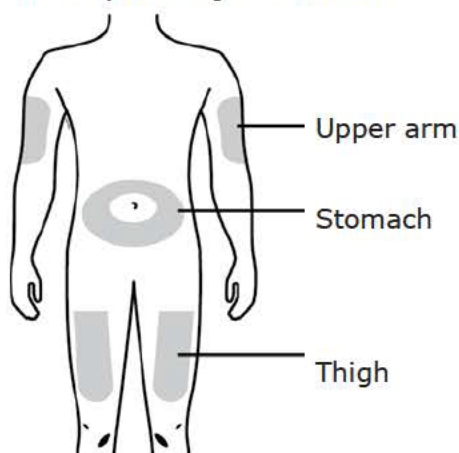
Wash your hands thoroughly with soap and water.

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

- New autoinjector
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container (see Step 4: Finish)



1D Prepare and clean your injection site.



You can use:

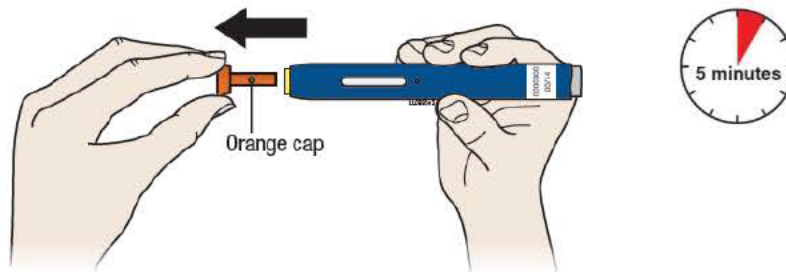
- Thigh
- Stomach (abdomen), except for a **two** inch area around your belly button
- Outer area of upper arm (only if someone else is giving you the injection)

Clean your 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 want to use the same injection site, make sure it is not the same spot you used for the last injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard.

Step 2: Get ready

- 2A** Pull the orange cap 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.



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

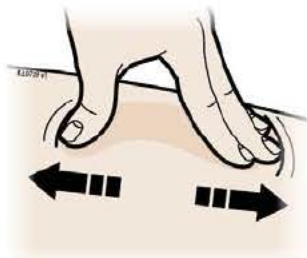
- **Do not** twist, bend, or wiggle the orange cap.
- **Do not** put the orange cap back onto the autoinjector.
- **Do not** put fingers into the yellow safety guard.
- **Do not** remove the orange cap from the autoinjector until you are ready to inject.

If you are unable to inject, please contact your healthcare provider.

- 2B** Stretch or pinch your injection site to create a firm surface.

Thigh:

Stretch method

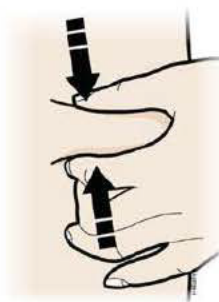


Stretch the skin firmly by moving your thumb and fingers in opposite directions, creating an area about **two** inches wide.

or

Stomach or upper arm:

Pinch method

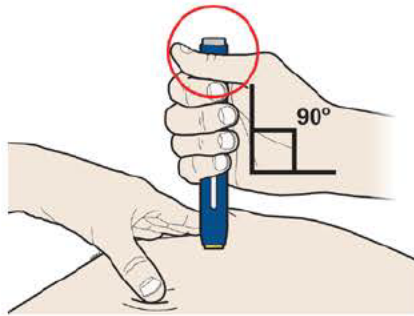


Pinch the skin firmly between your thumb and fingers, creating an area about **two** inches wide.

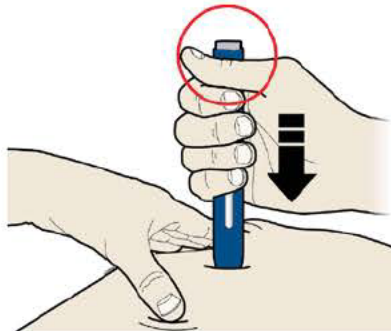
Important: It is important to keep skin stretched or pinched while injecting.

Step 3: Inject

- 3A** Hold the stretch or pinched skin. With the orange cap off, **place** autoinjector on the skin at 90 degrees. Do not touch the gray start button yet.

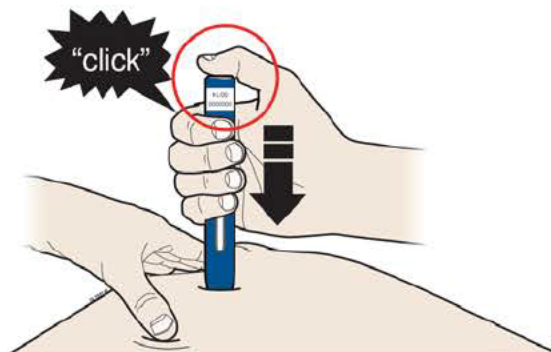


- 3B** Firmly **push** down the autoinjector onto the skin until it stops moving.

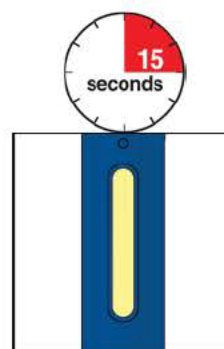
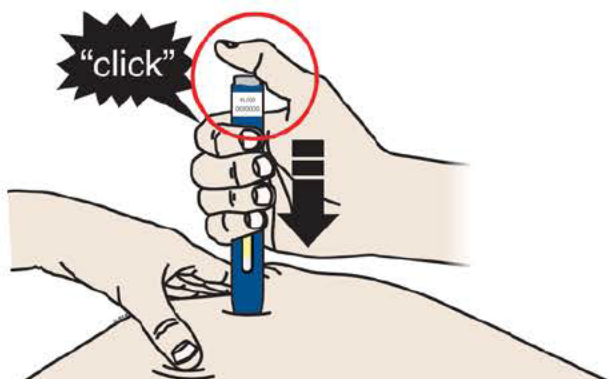


Important: You must push all the way down but **do not** touch the gray start button until you are ready to inject.

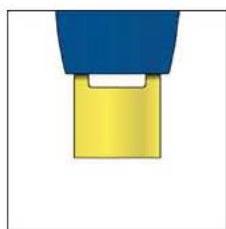
- 3C** When you are ready to inject, **press** the gray start button. You will hear a click.



3D Keep **pushing** the autoinjector down on your skin. Then **lift** your thumb while still holding the autoinjector on your skin. Your injection could take about 15 seconds.



Window turns from clear to yellow when the injection is done. You may hear a second click.



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

Important: When you remove the autoinjector, if the window has not turned yellow, or if it looks like the medicine is still injecting, this means you have not received a full dose. Call your healthcare provider immediately.

Step 4: Finish

4A Throw away the used autoinjector and orange needle cap.



Put the used autoinjector and orange needle cap in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the autoinjector or orange cap in your household trash.

If you do not have a FDA-cleared 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 state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- **Do not** reuse the autoinjector.
- **Do not** recap the autoinjector or put fingers into the yellow safety guard.

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

4B Check the injection site.

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

Do not rub the injection site.

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, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

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

AMGEN®

Manufactured by:

Amgen Inc.

Thousand Oaks, CA 91320-1799

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<part number> Revised: XX/XXXX vX

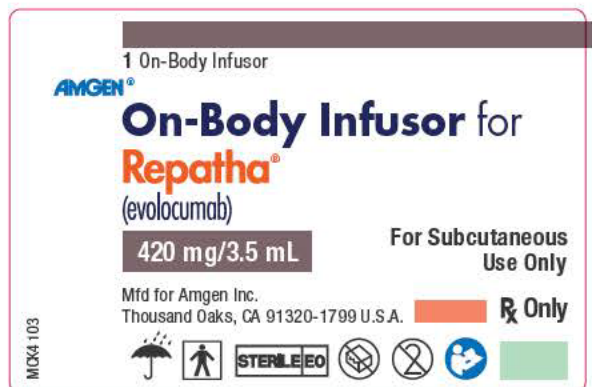
Repatha®
(evolcumab)
Injection
450 mg/3.5 mL (120 mg/mL)
For Subcutaneous Use Only
Single-Dose Only
Amgen Inc.

LOT
Exp.

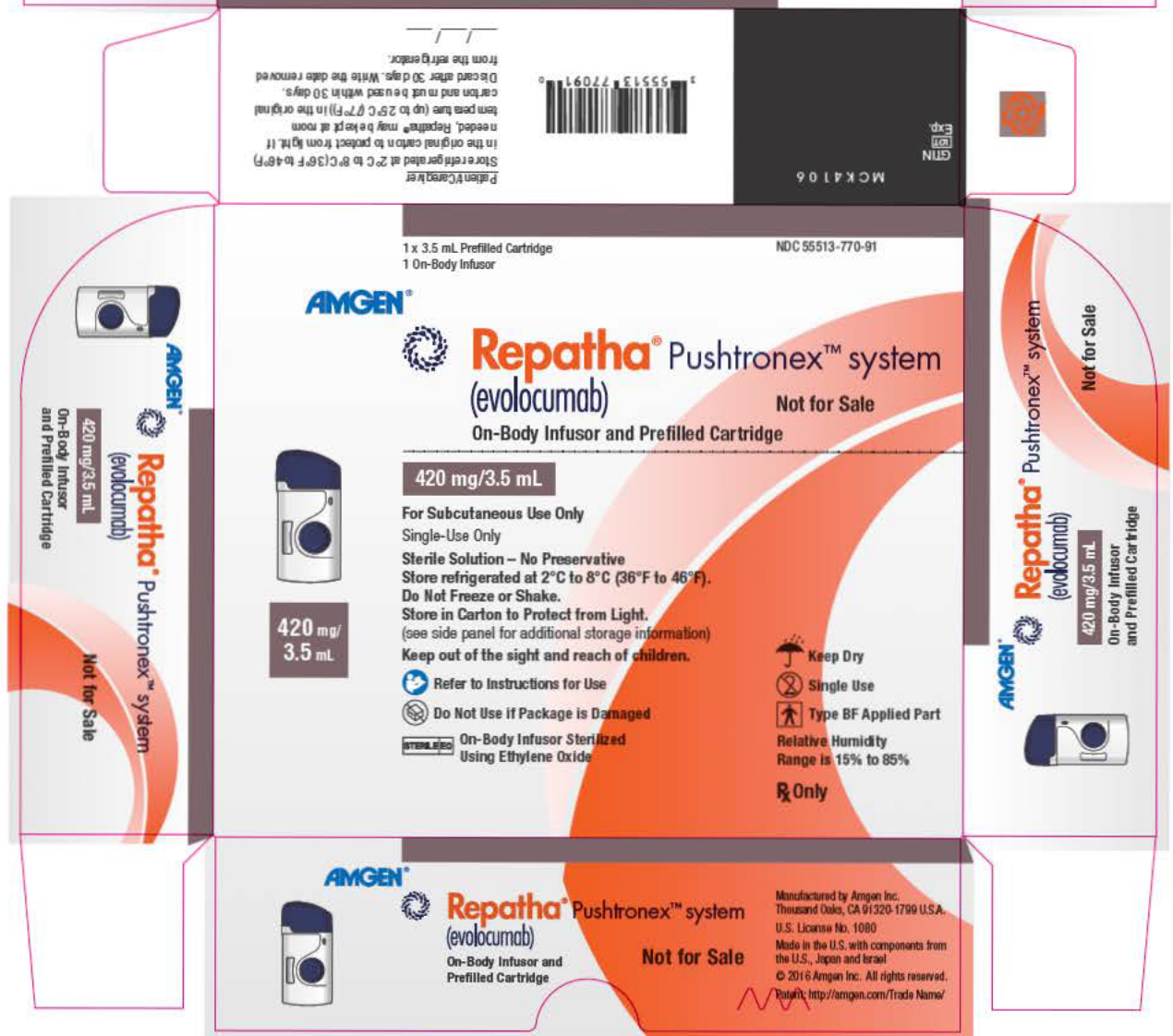
Date of

MCK4105

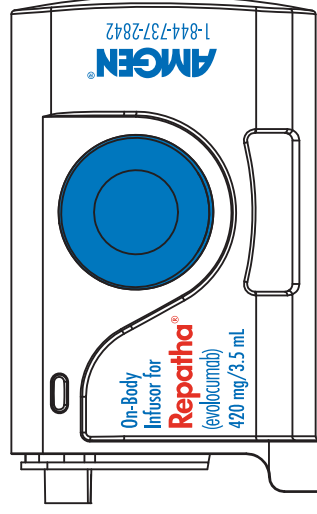
Reference ID: 3956545



Reference ID: 3956545



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Reference ID: 3956545

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/s/

JAMES P SMITH
07/08/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125522Orig1s004

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 21, 2016

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Ankur Kaola, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): REPATHA (evolocumab)

Dosage Form and Route: Injection for subcutaneous use

Application Type/Number: BLA 125522

Supplement Number: S-004

Applicant: Amgen, Inc.

1 INTRODUCTION

On February 29, 2016 Amgen, Inc. submitted for the Agency's review a Changes Being Effected (CBE) for the Instructions for Use (IFU) for the REPATHA SureClick Autoinjector, updated with additional user instructions to support proper drug administration with the autoinjector. Additional updates were made throughout the IFU to align content with the Amgen platform SureClick autoinjector IFU. REPATHA (evolocumab) injection for subcutaneous use was originally approved August 27, 2015 and is indicated as adjunct to diet and :

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C)
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on March 2, 2016, and June 17, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for REPATHA (evolocumab) injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft REPATHA (evolocumab) IFU received on February 29, 2016, and received by DMPP on June 13, 2016.
- Draft REPATHA (evolocumab) IFU received on February 29, 2016, and received by OPDP on June 17, 2016.
- REPATHA (evolocumab) Prescribing Information (PI) approved on August 27, 2015.
- Approved ENBREL (etanercept) SureClick autoinjector IFU comparator dated March 20, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

18 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS)
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/s/

AMANPREET K SARAI
06/21/2016

ANKUR S KALOLA
06/21/2016

MARCIA B WILLIAMS
06/21/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125522Orig1s004

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

From: Johnson, Kati
To: [Rupert, Adam \(arupert@amgen.com\)](mailto:arupert@amgen.com)
Cc: [Johnson, Kati \(Kati.Johnson@fda.hhs.gov\)](mailto:Kati.Johnson@fda.hhs.gov)
Subject: BLA 125522/S-004, revised IFU for AI
Date: Thursday, June 30, 2016 2:46:00 PM
Attachments: [125522_S004 revised IFU to firm 6 30.docx](#)

Here you go. We are down to a couple of points of disagreement
Please confirm receipt.
Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

9 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS)
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/s/

KATI JOHNSON
07/05/2016

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning
meeting****

TO:
CDER-OPDP-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Division of Metabolism and Endocrinology Products
PM=Kati Johnson, 6-1234

REQUEST DATE:
6/17/2016

IND NO.

BLA NO.
125522/S-004

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Repatha (evolocumab)

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up
meeting)

7/6/2016***

NAME OF FIRM:
Amgen

PDUFA Date: 8/29/2016

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- ☐ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
X INSTRUCTIONS FOR USE (IFU)

Patient labeling will contact you
when their review is near
completed per your normal
process

TYPE OF APPLICATION/SUBMISSION

- ☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT

- ☐ INITIAL PROPOSED LABELING
XLABELING REVISION

For OSE USE ONLY

- ☐ REMS

EDR link to submission: [\\CDSESUB1\evsprod\BLA125522\0115](#)

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: N/A Labeling Meetings: N/A Wrap-Up Meeting: N/A

***This supplement involves minor revisions to the IFU for the SureClick autoinjector. Although this is not due until the end of August, we are trying to approve this supplement along with S-001 (new device) by 7/8/2016 if possible. Patient labeling has they should complete their review by the end of the month. The firm has made very few revisions, and the supplement was appropriately submitted as a CBE. Since these were safety changes, I didn't think to involve you all. Sorry. If approving this early will result in a hardship for you all, then we can fall back to the 8/29/2016 goal date. Thanks for your help.

SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND

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/s/

KATI JOHNSON
06/17/2016



BLA 125522/S-004

**CBE LABELING SUPPLEMENT –
ACKNOWLEDGEMENT**

Amgen
Attention: Adam Rupert
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799

Dear Mr. Rupert:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: BLA 125522/S-004

PRODUCT NAME: Repatha (evolocumab) injection, 140 mg/mL

DATE OF SUBMISSION: February 29, 2016

DATE OF RECEIPT: February 29, 2016

This supplemental application, submitted as a “Special Labeling Supplement – Changes Being Effected as described under 21 CFR 601.12(f)(2), proposes to revise the Instructions for Use (IFU) for the SureClick® Autoinjector. Specifically, text and pictures have been added to convey that upon removal of the orange cap, the product should be injected within 5 minutes, and associated minor revisions. Continued use of the change is subject to our final approval of this supplement.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 29, 2016 in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be August 29, 2016.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or

courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
03/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION				
TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Metabolism and Endocrinology Products PM=Kati Johnson, 6-1234				
REQUEST DATE: 3/2/2016	BLA NO.: 125522/S-004	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)				
NAME OF DRUG: Repatha (evolocumab) injection	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) 7/15/2016			
SPONSOR: Amgen		PDUFA Date: 8/29/2016				
TYPE OF LABEL TO REVIEW						
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU) </td> <td style="width: 33%; vertical-align: top;"> TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION </td> <td style="width: 33%; vertical-align: top;"> REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION </td> </tr> </table>				TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
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EDR link to submission: \\CDSESUB1\evsprod\BLA125522\0115						
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.						
<p> COMMENTS/SPECIAL INSTRUCTIONS: This product is available as a prefilled syringe and an autoinjector for the treatment of dyslipidemia. The firm is revising the IFU of the SureClick® autoinjector because they have identified that some patients are removing the outside orange cap and then NOT promptly injecting the product. According to them, the drug product can then dry inside the needle (b) (4). The firm has provided a marked-up PDF copy as well as a CLEAN WORD copy of the proposed IFU. The currently approved IFU is that which was approved with the BLA on 8/27/2015. </p> <p> PLEASE PROVIDE THE NAME OF THE ASSIGNED REVIEWER. THANKS VERY MUCH FOR YOUR ASSISTANCE. </p> <p> Filing/Planning Meeting: [Insert Date(s)]-N/A Mid-Cycle Meeting: [Insert Date]-N/A Labeling Meetings: [Insert Dates]-N/A Wrap-Up Meeting: [Insert Date]-N/A </p>						
SIGNATURE OF REQUESTER						

Kati Johnson, Senior Regulatory Project Manager		
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only)	XDARRTS

Version: 12/9/2011

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/s/

KATI JOHNSON
03/02/2016