# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 125522Orig1s045

| | |
|---|---|
| ***Trade Name:*** | REPATHA |
| ***Generic or Proper Name:*** | evolocumab |
| ***Sponsor:*** | Amgen Inc. |
| ***Approval Date:*** | August 21, 2025 |
| ***Indication:*** | REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor indicated:<br>•To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults at increased risk for these events.<br>•As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in:<br>o adults with hypercholesterolemia.<br>o adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).<br>o adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH). |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# 125522Orig1s045

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125522Orig1s045

# APPROVAL LETTER

BLA 125522/S-045

**SUPPLEMENT APPROVAL**

Amgen Inc.
Attention: Anusha Ponnuru, PharmD
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Ponnuru:

Please refer to your supplemental biologics license application (sBLA) received December 19, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Repatha (evolocumab) injection.

This Prior Approval sBLA provides for changes to the SureClick autoinjector Instructions for Use, Reference Guide, and carton labeling to improve organization and clarity of instructions.

This Prior Approval sBLA also provides for changes to the Prescribing Information to update Section 1 *Indications and Usage* to revise the indication.

The Patient Package Insert was revised to reflect the changes to the Prescribing Information.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- Recent Major Changes and Revision dates in the Highlights of Prescribing Information updated to reflect supplement approval.

## 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 FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information,

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Patient Package Insert, and Instructions for Use) 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on August 14, 2025, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 125522/S-045**." Approval of this submission by FDA is not required before the labeling is used.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 supplement application, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]
You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

## 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).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Ron Picking, Regulatory Project Manager, at 240-402-3211 or ronald.pickingiii@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

John Sharretts, MD
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Latex-containing autoinjector Instructions for Use
  - Latex-free autoinjector Instructions for Use
  - Latex-containing prefilled syringe Instructions for Use (version approved November 20, 2024)
  - Latex-free prefilled syringe Instructions for Use (version approved November 20, 2024)
- Reference Guide
- Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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JOHN M SHARRETTS
08/21/2025 02:34:09 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125522Orig1s045

# 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----------**

| | |
|---|---|
| Indications and Usage (1) | 08/2025 |
| Dosage and Administration (2.3) | 11/2024 |
| Warnings and Precautions (5.1) | 11/2024 |

**----------INDICATIONS AND USAGE----------**

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

- To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults at increased risk for these events. (1)
- As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in:
  - adults with hypercholesterolemia. (1)
  - adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH). (1)
  - adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH). (1)

**----------DOSAGE AND ADMINISTRATION----------**

In adults at increased risk for CV events or with hypercholesterolemia:
- The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously. (2.1)
- If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen. (2.1)

In adults and pediatric patients aged 10 years and older with HeFH:
- The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously. (2.1)
- If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen. (2.1)

In adults and pediatric patients aged 10 years and older with HoFH:
- The initial recommended dosage of REPATHA is 420 mg once monthly administered subcutaneously. (2.1)
- The dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. (2.1)
- Patients on lipid apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule. Administer REPATHA after the apheresis session is complete. (2.1)
- Assess LDL-C when clinically appropriate. The LDL-lowering effect of REPATHA may be measured as early as 4 weeks after initiation. (2.1)
- REPATHA is available as prefilled single-dose SureClick® autoinjectors and prefilled single-dose syringes that either contain dry natural rubber (a derivative of latex) in the needle cover or are not made with natural rubber latex. Consider prescribing a presentation of REPATHA that does not contain dry natural rubber for individuals that are sensitive to latex. (2.3, 16)
- Administer REPATHA subcutaneously into areas of the abdomen, thigh, or upper arm. Rotate injection sites for each administration. (2.3)
- See Full Prescribing Information for important administration instructions. (2.3)

**----------DOSAGE FORMS AND STRENGTHS----------**

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

**----------CONTRAINDICATIONS----------**

Patients with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients in REPATHA. (4)

**----------WARNINGS AND PRECAUTIONS----------**

Hypersensitivity Reactions: Angioedema has occurred. If signs or symptoms of serious hypersensitivity 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 (> 5% of patients treated with REPATHA and more frequently than placebo) adverse reactions in adults with:
*Primary hypercholesterolemia:* nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. (6)
*Established CVD:* diabetes mellitus, nasopharyngitis and upper respiratory tract infection. (6)

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

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

**Revised: 08/2025**

**FULL PRESCRIBING INFORMATION: CONTENTS***



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

**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

REPATHA is indicated:

- To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults at increased risk for these events.
- As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in:
    - adults with hypercholesterolemia.
    - adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
    - adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

- In adults at increased risk for CV events or with hypercholesterolemia:
    - The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously *[see Dosage and Administration (2.3)]*.
    - If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.
- In adults and pediatric patients aged 10 years and older with HeFH:
    - The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously *[see Dosage and Administration (2.3)]*.
    - If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.
- In adults and pediatric patients aged 10 years and older with HoFH:
    - The initial recommended dosage of REPATHA is 420 mg once monthly administered subcutaneously *[see Dosage and Administration (2.3)]*.
    - The dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks.
    - Patients on lipid apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule. Administer REPATHA after the apheresis session is complete.
- Assess LDL-C when clinically appropriate. The LDL-lowering effect of REPATHA may be measured as early as 4 weeks after initiation.
- When monitoring LDL-C for patients receiving REPATHA 420 mg once monthly, note that LDL-C can vary during the dosing interval in some patients; recommend measuring LDL-C just prior to the next scheduled dose *[see Clinical Studies (14)]*.

### 2.2 Missed Doses

If a dose is missed:

- Within 7 days from the missed dose, instruct the patient to administer REPATHA and resume the patient's original schedule.

- More than 7 days after the missed dose:
    - For an every 2-week dose, instruct the patient to wait until the next dose on the original schedule.
    - For a once-monthly dose, instruct the patient to administer the dose and start a new schedule based on this date.

### 2.3 Important Administration Instructions

- REPATHA is available as prefilled single-dose SureClick® autoinjectors and prefilled single-dose syringes that either contain dry natural rubber (a derivative of latex) in the needle cover or are not made with natural rubber latex *[see How Supplied/Storage and Handling (16)]*. Consider prescribing a presentation of REPATHA that does not contain dry natural rubber for individuals that are sensitive to latex *[see Warnings and Precautions (5.1)]*.
- Train patients and/or caregivers on how to prepare and administer REPATHA, according to the Instructions for Use and instruct them to read and follow the Instructions for Use each time they use REPATHA.
- Prior to use, allow REPATHA to warm to room temperature for at least 30 minutes for the prefilled single-dose SureClick® autoinjector or prefilled single-dose syringe and for at least 45 minutes for the on-body infusor with prefilled cartridge if REPATHA has been refrigerated *[see How Supplied/Storage and Handling (16)]*.
- Visually inspect REPATHA prior to administration. REPATHA is a clear to opalescent, colorless to pale yellow solution. Do not use if the solution is cloudy, discolored, or contains particles.
- Administer REPATHA subcutaneously into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. Avoid injecting into areas with scars or stretch marks. Rotate injection sites for each administration.
- The 420 mg dose of REPATHA can be administered:
    - over 5 minutes by using the single-dose on-body infusor with prefilled cartridge, or
    - by giving 3 injections consecutively within 30 minutes using the prefilled single-dose SureClick® autoinjector or prefilled single-dose syringe.

## 3 DOSAGE FORMS AND STRENGTHS

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

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

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema, have been reported in patients treated with REPATHA. If signs or symptoms of serious hypersensitivity reactions occur, discontinue treatment with REPATHA, treat according to the standard of care, and monitor until signs and symptoms resolve. REPATHA is contraindicated in patients with a history of serious hypersensitivity reactions to evolocumab or any excipient in REPATHA *[see Contraindications (4)]*.

The prefilled single-dose SureClick® autoinjector and prefilled single-dose syringe presentations of REPATHA that contain dry natural rubber (a derivative of latex) in the needle cover may cause an allergic reaction in individuals sensitive to latex. Instruct patients to inform their healthcare provider if they are sensitive to latex. Consider prescribing a presentation of REPATHA that does not contain dry natural rubber for individuals that are sensitive to latex *[see How Supplied/Storage and Handling (16)]*.

## 6 ADVERSE REACTIONS

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

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

### 6.1 Clinical Trials Experience

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

Adverse Reactions in Adults with Primary Hypercholesterolemia

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

*Adverse Reactions in a 52-Week Controlled Trial*

In a 52-week, double-blind, randomized, placebo-controlled trial, 599 patients received 420 mg of REPATHA subcutaneously once monthly *[see Clinical Studies (14)]*. The mean age was 56 years (range: 22 to 75 years), 23% were older than 65 years, 52% women, 80% White, 8% Black, 6% Asian; 6% identified as Hispanic ethnicity. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients 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 ≥ 3% of REPATHA-treated Patients and More Frequently than with Placebo in a 52-Week Trial**

| | **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; 5% identified as Hispanic ethnicity. Adverse reactions reported in at least 1% of REPATHA-treated patients, and more frequently than in placebo-treated patients, are shown in Table 2.

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

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

| | **Placebo** (N = 1224) % | **REPATHA**† (N = 2052) % |
|---|---|---|
| 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 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.

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

Adverse Reactions in the Cardiovascular Outcomes Trial
In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial, 27,525 patients received at least one dose of REPATHA or placebo *[see Clinical Studies (14)]*. The mean age was 62.5 years (range: 40 to 86 years), 45% were 65 years or older, 9% were 75 years or older, 25% women, 85% White, 2% Black and 10% Asian; 8% identified as Hispanic ethnicity. Patients were exposed to REPATHA or placebo for a median of 24.8 months; 91% of patients were exposed for ≥ 12 months, 54% were exposed for ≥ 24 months and 5% were exposed for ≥ 36 months.

The safety profile of REPATHA in this trial was generally consistent with the safety profile described above in the 12- and 52-week controlled trials involving patients with primary hypercholesterolemia. Common adverse reactions (> 5% of patients treated with REPATHA and occurring more frequently than placebo) included diabetes mellitus (8.8% REPATHA, 8.2% placebo), nasopharyngitis (7.8% REPATHA, 7.4% placebo), and upper respiratory tract infection (5.1% REPATHA, 4.8% placebo).

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

Adverse Reactions in Pediatric Patients with HeFH
In a 24-week, randomized, placebo-controlled, double-blind trial of 157 pediatric patients with HeFH, 104 patients received 420 mg REPATHA subcutaneously once monthly *[see Clinical Studies (14)]*. The mean age was 13.7 years (range: 10 to 17 years), 56% were female, 85% White, 1% Black, 1% Asian, and 13% other; 8% identified as Hispanic ethnicity. Common adverse reactions (> 5% of patients treated with REPATHA and occurring more frequently than placebo) included:

- Nasopharyngitis (12% versus 11%)
- Headache (11% versus 2%)

- Oropharyngeal pain (7% versus 0%)
- Influenza (6% versus 4%)
- Upper respiratory tract infection (6% versus 2%)

Adverse Reactions in Adults and Pediatric Patients with HoFH
In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH, 33 patients received 420 mg of REPATHA subcutaneously once monthly *[see Clinical Studies (14)]*. 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%)

In a multicenter, open-label 5-year extension study, 106 patients with HoFH, including 14 pediatric patients, received 420 mg of REPATHA subcutaneously once monthly or every 2 weeks *[see Clinical Studies (14)]*. The mean age was 34 years (range: 13 to 68 years), 51% were women, 80% White, 12% Asian, 1% Native American, and 7% other; 5% identified as Hispanic ethnicity. No new adverse reactions were observed during the open-label extension study.

### 6.2 Immunogenicity

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

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

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

The development of anti-evolocumab antibodies was not detected in clinical trials of pediatric patients treated with REPATHA.

There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of REPATHA.

### 6.3 Postmarketing Experience

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

- Hypersensitivity reactions: Angioedema
- Influenza-like illness

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Available data from clinical trials and postmarketing reports on REPATHA use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. 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. Monoclonal antibodies are transported across the placenta in increasing amounts especially near term; therefore, evolocumab has the potential to be transmitted from the mother to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. 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.

There is a pregnancy safety study for REPATHA. If REPATHA is administered during pregnancy, healthcare providers should report REPATHA exposure by contacting Amgen at 1-800-77-AMGEN (1-800-772-6436) or https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting.

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. 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. 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.

### 8.4 Pediatric Use

The safety and effectiveness of REPATHA in combination with diet and other LDL-C-lowering therapies for the treatment of HoFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is supported by evidence from an adequate and well-controlled trial in adults and pediatric patients aged 13 years and older with HoFH (including 7 pediatric patients treated with REPATHA) and from open-label studies which included an additional 19 pediatric patients aged 11 years and older with HoFH not previously treated with REPATHA *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

The safety and effectiveness of REPATHA as an adjunct to diet and other LDL-C-lowering therapies for the treatment of HeFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is based on data from a 24-week, randomized, placebo-controlled, double-blind trial in pediatric patients with HeFH. In the trial, 104 patients received REPATHA 420 mg subcutaneously once monthly and 53 patients received placebo; 39 patients (25%) were 10 to 11 years of age *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

The safety and effectiveness of REPATHA have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years old or in pediatric patients with other types of hypercholesterolemia.

### 8.5 Geriatric Use

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

### 8.6 Renal Impairment

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

### 8.7 Hepatic Impairment

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

## 11 DESCRIPTION

Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) directed against human proprotein convertase subtilisin kexin type 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 use. Each 1 mL prefilled single-dose SureClick® autoinjector and prefilled single-dose syringe 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-dose 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 type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptor (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. 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. Maximum LDL-C reduction occurred by 2 weeks after a single-dose of 140 mg of evolocumab and by 3 weeks after a single-dose of 420 mg of evolocumab.

### 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 of 18.6 µg/mL and $AUC_{last}$ mean of 188 day•µg/mL. Administration of the 420 mg dose in healthy volunteers resulted in a $C_{max}$ mean of 59.0 µg/mL and $AUC_{last}$ mean of 924 day•µg/mL. Following a single 420 mg intravenous dose, the mean systemic clearance was estimated to be 12 mL/hr. An approximate 2- to 3-fold accumulation was observed in trough serum concentrations ($C_{min}$ 7.21) following 140 mg doses administered subcutaneously every 2 weeks or following 420 mg doses administered subcutaneously monthly ($C_{min}$ 11.2), 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 steady-state volume of distribution was estimated to be 3.3 L.

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.

*Pediatric Patients*
The pharmacokinetics of REPATHA were evaluated in 103 pediatric patients aged 10 to 17 years with HeFH (Study 6) *[see Use in Specific Populations (8.4), and Clinical Studies (14)]*. Following subcutaneous administration of 420 mg REPATHA once monthly, mean trough serum concentrations were 22.4 mcg/mL and 25.8 mcg/mL over the Week 12 and Week 24 time points, respectively. The pharmacokinetics of REPATHA were evaluated in 12 pediatric patients aged 11 to 17 years with HoFH (Study 9) *[see Use in Specific Populations (8.4), and Clinical Studies (14)]*. Following subcutaneous administration of 420 mg REPATHA once monthly, mean serum trough concentrations were 20.3 mcg/mL and 17.6 mcg/mL at Week 12 and Week 80, respectively.

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

In a clinical trial of 18 patients with either normal renal function (estimated glomerular filtration rate [eGFR] $\geq$ 90 mL/min/1.73 $m^2$, n = 6), severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$, n = 6), or end-stage renal disease (ESRD) receiving hemodialysis (n = 6), exposure to evolocumab after a single 140 mg subcutaneous dose was decreased in patients with severe renal impairment or ESRD receiving hemodialysis. Reductions in PCSK9 levels in patients with severe renal impairment or ESRD receiving hemodialysis was similar to those with normal renal function *[see Use in Specific Populations (8.6)]*.

*Hepatic Impairment*
Following a single 140 mg subcutaneous dose of evolocumab in patients with mild or moderate hepatic impairment, a 20-30% lower mean $C_{max}$ and 40-50% lower mean AUC were observed as compared to healthy patients *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies
An approximately 20% decrease in the $C_{max}$ and AUC of evolocumab was observed in adult patients co-administered with a high-intensity statin regimen. This difference is not clinically meaningful.

## 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

Adult Patients with Established Cardiovascular Disease

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

The mean (SD) age at baseline was 63 (9) years, with 45% being at least 65 years old; 25% were women. The trial population was 85% White, 2% Black, and 10% Asian; 8% identified as Hispanic ethnicity. Regarding prior diagnoses of cardiovascular disease, 81% had prior myocardial infarction, 19% prior non-hemorrhagic stroke, and 13% had symptomatic peripheral arterial disease. Selected additional

baseline risk factors included hypertension (80%), diabetes mellitus (1% type 1; 36% type 2), current daily cigarette smoking (28%), New York Heart Association class I or II congestive heart failure (23%), and eGFR < 60 mL/min per 1.73 $m^2$ (6%). Most patients were on a high- (69%) or moderate-intensity (30%) statin therapy at baseline, and 5% were also taking ezetimibe. Most patients were taking at least one other cardiovascular medication including anti-platelet agents (93%), beta blockers (76%), angiotensin converting enzyme (ACE) inhibitors (56%), or angiotensin receptor blockers (23%). On stable background lipid-lowering therapy, the median [Q1, Q3] LDL-C at baseline was 92 [80, 109] mg/dL; the mean (SD) was 98 (28) mg/dL.

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

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

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

| | **Placebo** | | **REPATHA** | | **REPATHA vs. Placebo** |
|---|---|---|---|---|---|
| | **N = 13780 n (%)** | **Incidence Rate (per 100 patient years)** | **N = 13784 n (%)** | **Incidence Rate (per 100 patient years)** | **Hazard Ratio (95% CI)** |
| Primary composite endpoint | | | | | |
| Time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina | 1563 (11.3) | 5.2 | 1344 (9.8) | 4.5 | 0.85 (0.79, 0.92) |
| Key secondary composite endpoint | | | | | |
| Time to first occurrence of cardiovascular death, myocardial infarction, stroke | 1013 (7.4) | 3.4 | 816 (5.9) | 2.7 | 0.80 (0.73, 0.88) |
| Other secondary endpoints | | | | | |
| Time to cardiovascular death | 240 (1.7) | 0.8 | 251 (1.8) | 0.8 | 1.05 (0.88, 1.25) |
| Time to death by any cause[a] | 426 (3.1) | 1.4 | 444 (3.2) | 1.5 | 1.04 (0.91, 1.19) |
| Time to first fatal or non-fatal myocardial infarction | 639 (4.6) | 2.1 | 468 (3.4) | 1.6 | 0.73 (0.65, 0.82) |
| Time to first fatal or non-fatal stroke | 262 (1.9) | 0.9 | 207 (1.5) | 0.7 | 0.79 (0.66, 0.95) |

| | Placebo | | REPATHA | | REPATHA vs. Placebo |
|---|---|---|---|---|---|
| | N = 13780 n (%) | Incidence Rate (per 100 patient years) | N = 13784 n (%) | Incidence Rate (per 100 patient years) | Hazard Ratio (95% CI) |
| Time to first coronary revascularization | 965 (7.0) | 3.2 | 759 (5.5) | 2.5 | 0.78 (0.71, 0.86) |
| Time to first hospitalization for unstable angina[b] | 239 (1.7) | 0.8 | 236 (1.7) | 0.8 | 0.99 (0.82, 1.18) |

[a] Time to death by any cause is not a component of either the primary composite endpoint or key secondary composite endpoint.
[b] Not a prespecified endpoint; an *ad hoc* analysis was performed to ensure results are provided for each individual component of the primary endpoint.

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

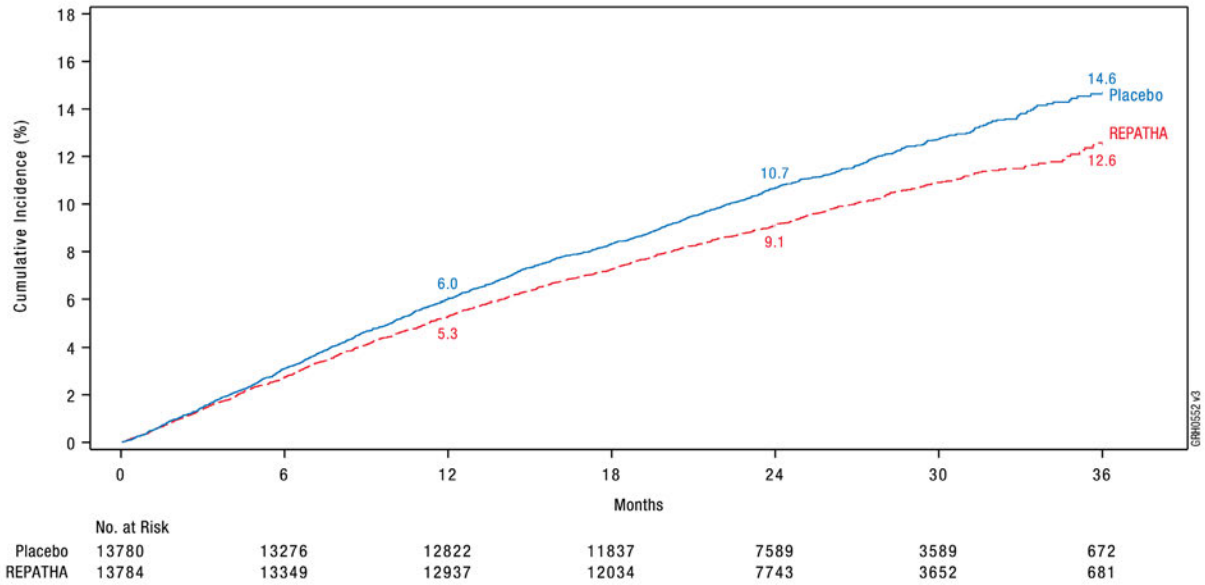
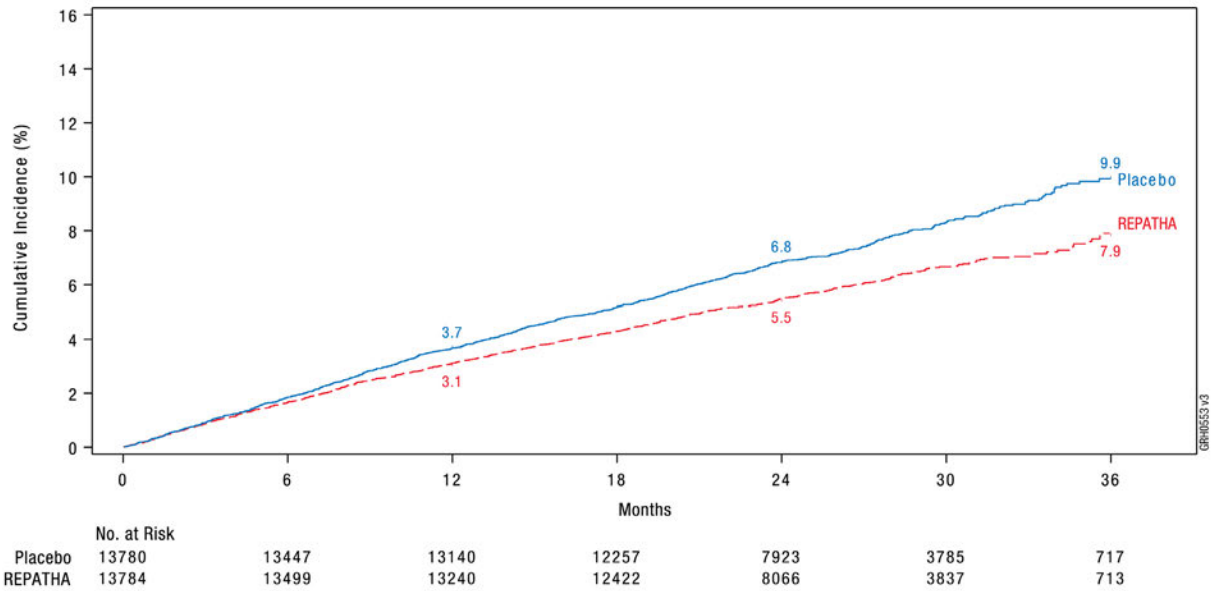


**Figure 2. Estimated Cumulative Incidence of Key Secondary Composite Endpoint Over 3 Years in FOURIER**




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

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

Primary Hypercholesterolemia

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

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

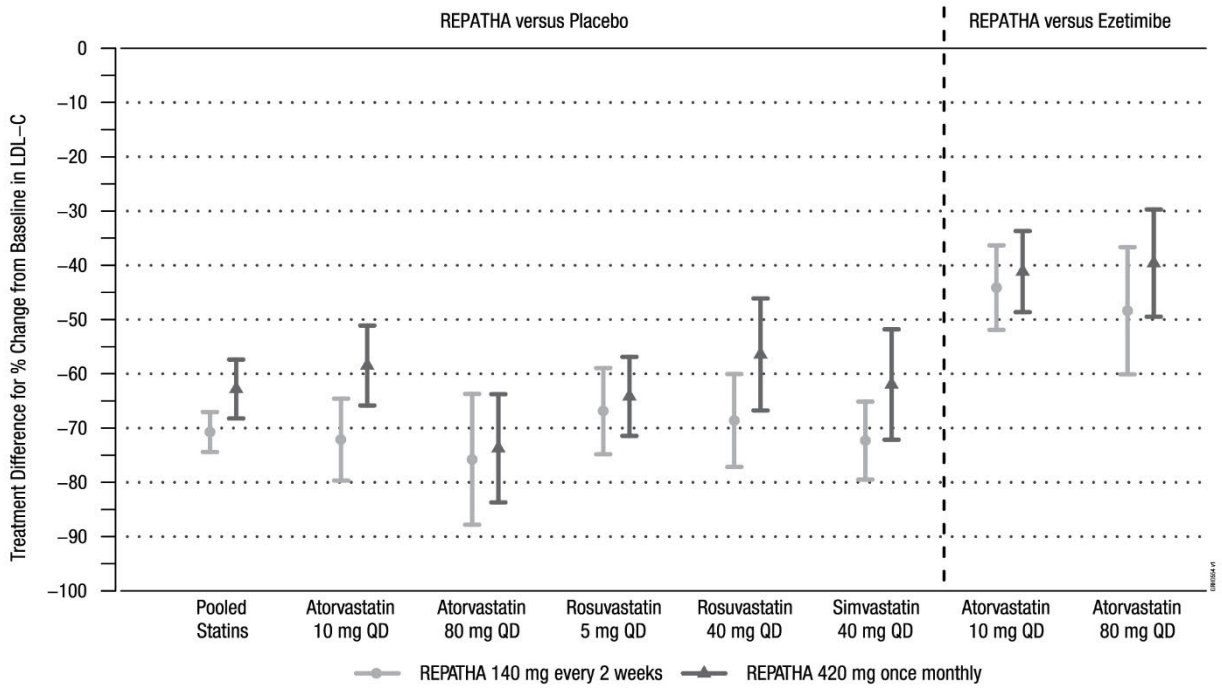
**Table 4. Effect of REPATHA on Lipid Parameters in Patients with Hypercholesterolemia on Background Statin Regimens (Mean % Change from Baseline to Week 12 in LAPLACE-2)**

| Treatment Group | LDL-C | Non-HDL-C | Apo B | Total Cholesterol |
|---|---|---|---|---|
| **REPATHA every 2 weeks vs. Placebo every 2 weeks (Background statin: atorvastatin 10 mg or 80 mg; rosuvastatin 5 mg or 40 mg; simvastatin 40 mg)** | | | | |
| Placebo every 2 weeks (n = 281) | 8 | 6 | 5 | 4 |
| REPATHA 140 mg every 2 weeks† (n = 555) | -63 | -53 | -49 | -36 |
| Mean difference from placebo (95% CI) | -71 (-74, -67) | -59 (-62, -55) | -55 (-58, -52) | -40 (-43, -38) |
| **REPATHA once monthly vs. Placebo once monthly (Background statin: atorvastatin 10 mg or 80 mg; rosuvastatin 5 mg or 40 mg; simvastatin 40 mg)** | | | | |
| Placebo once monthly (n = 277) | 4 | 5 | 3 | 2 |
| REPATHA 420 mg once monthly (n = 562) | -59 | -50 | -46 | -34 |
| Mean difference from placebo (95% CI) | -63 (-68, -57) | -54 (-58, -50) | -50 (-53, -47) | -36 (-39, -33) |
| **REPATHA every 2 weeks vs. Ezetimibe 10 mg daily (Background statin: atorvastatin 10 mg or 80 mg)** | | | | |
| Ezetimibe 10 mg daily (n = 112) | -17 | -16 | -14 | -12 |
| REPATHA 140 mg every 2 weeks† (n = 219) | -63 | -52 | -49 | -36 |
| Mean difference from Ezetimibe (95% CI) | -45 (-52, -39) | -36 (-41, -31) | -35 (-40, -31) | -24 (-28, -20) |
| **REPATHA once monthly vs. Ezetimibe 10 mg daily (Background statin: atorvastatin 10 mg or 80 mg)** | | | | |
| Ezetimibe 10 mg daily (n = 109) | -19 | -16 | -11 | -12 |
| REPATHA 420 mg once monthly (n = 220) | -59 | -50 | -46 | -34 |
| Mean difference from Ezetimibe (95% CI) | -41 (-47, -35) | -35 (-40, -29) | -34 (-39, -30) | -22 (-26, -19) |

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

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

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




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

Study 3 (DESCARTES, NCT01516879) was a multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 901 patients with hypercholesterolemia who received protocol-determined background lipid-lowering therapy of a cholesterol-lowering diet either alone or in addition to atorvastatin (10 mg or 80 mg daily) or the combination of atorvastatin 80 mg daily with ezetimibe. After stabilization on background therapy, patients were randomly assigned to the addition of placebo or REPATHA 420 mg administered subcutaneously once monthly. Overall, the mean age at baseline was 56 years (range: 25 to 75 years), 23% were ≥ 65 years, 52% women, 80% White, 8% Black, and 6% Asian; 6% identified as Hispanic or Latino ethnicity. After stabilization on the assigned background therapy, the mean baseline LDL-C ranged between 90 and 117 mg/dL across the four background therapy groups.

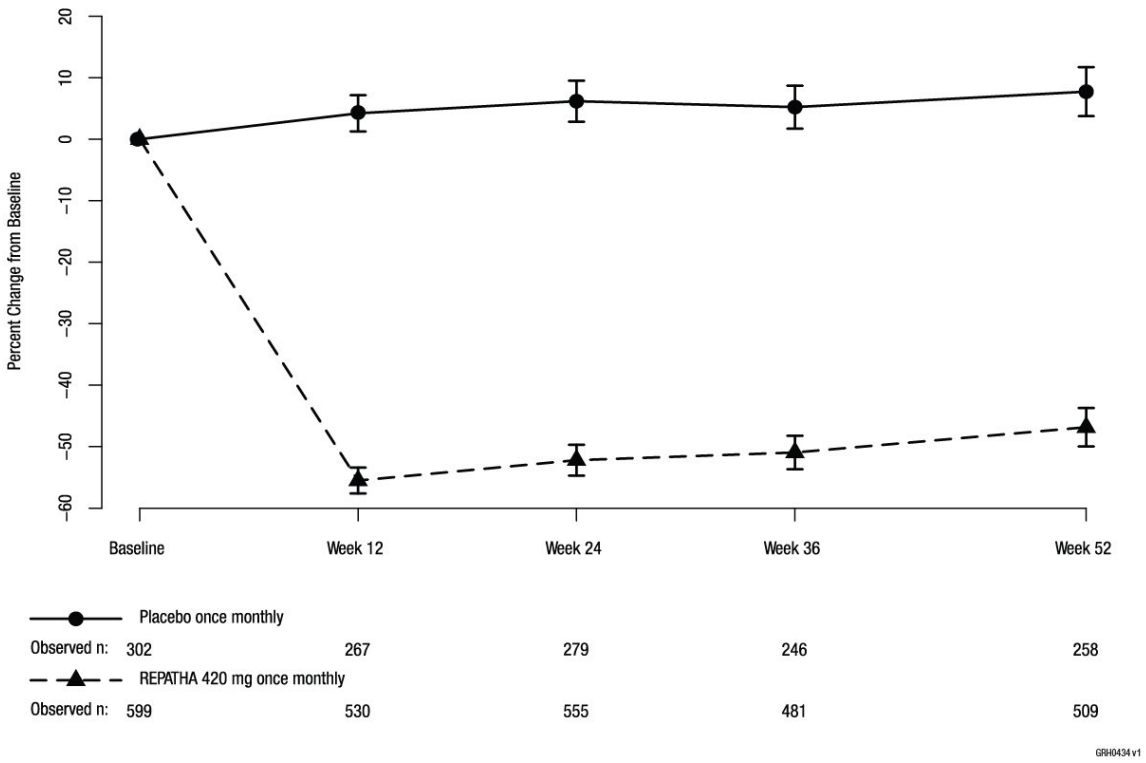
In these patients with hypercholesterolemia on a protocol-determined background therapy, the difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was −55% (95% CI: −60%, −50%; $p < 0.0001$) (Table 5 and Figure 4). For additional results,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

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

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

Estimates based on a multiple imputation model that accounts for treatment adherence
* Prior to randomization, patients were stabilized on background therapy consisting of a cholesterol-lowering diet either alone or in addition to atorvastatin (10 mg or 80 mg daily) or the combination of atorvastatin 80 mg daily with ezetimibe.

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




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

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

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

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

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

Estimates based on a multiple imputation model that accounts for treatment adherence
†140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

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

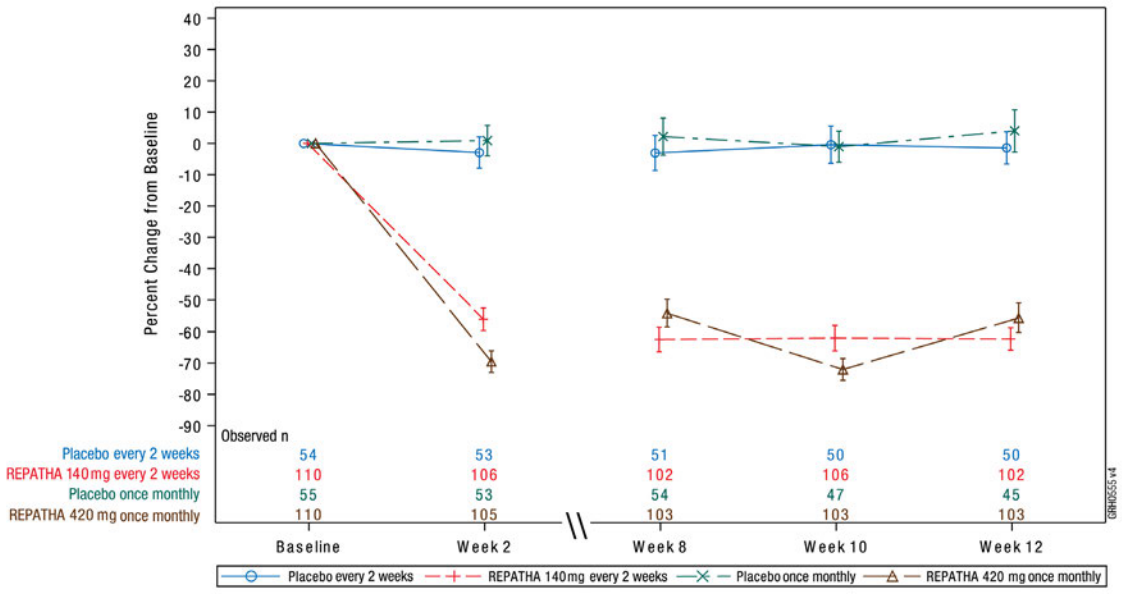
The differences between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was −61% (95% CI: −67%, −55%; p < 0.0001) and −60% (95% CI: −68%, −52%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results, see Table 7 and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

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

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

Estimates based on a multiple imputation model that accounts for treatment adherence
† 140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

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




N = number of patients randomized and dosed in the full analysis set
Estimates based on a multiple imputation model that accounts for treatment adherence
Error bars indicate 95% confidence intervals

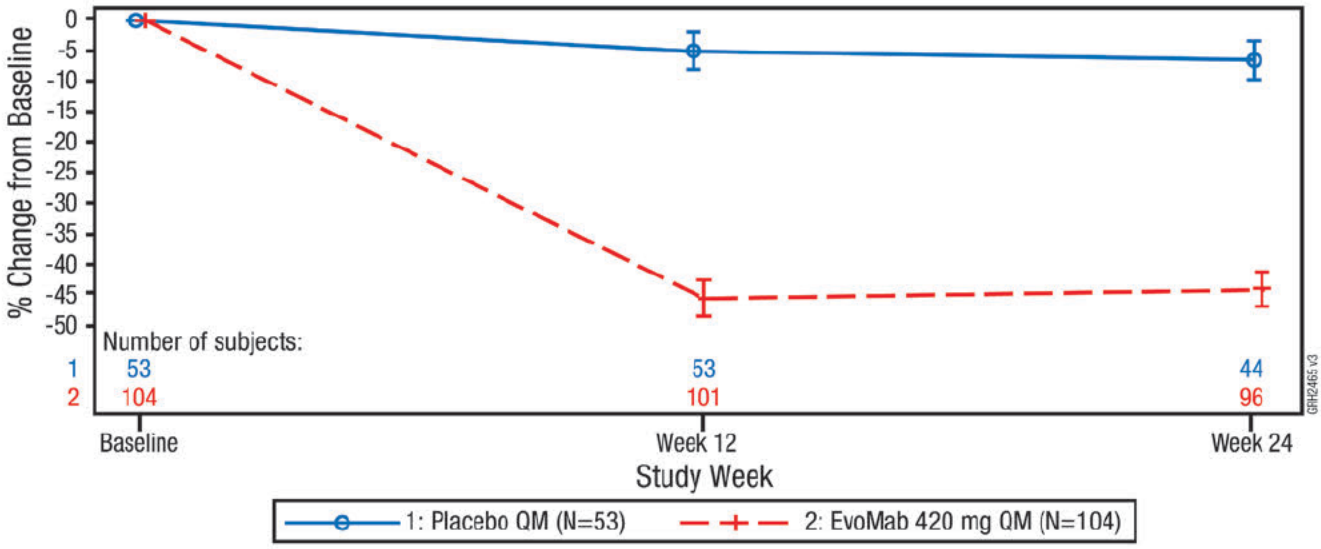
Pediatric Patients with HeFH

Study 6 (HAUSER-RCT, NCT02392559) was a randomized, multicenter, placebo-controlled, double-blind, 24-week trial in 157 pediatric patients aged 10 to 17 years with HeFH *[see Use in Specific Populations (8.4)]*. HeFH was diagnosed by diagnostic criteria for HeFH [Simon Broome Register Group (1991), the Dutch Lipid Clinic Network (1999), MEDPED (1993)] or by genetic testing. Patients were required to be on a low-fat diet and optimized background lipid-lowering therapy. Patients were randomly assigned 2:1 to receive 24 weeks of subcutaneous once monthly 420 mg REPATHA or placebo; 104 patients received REPATHA and 53 patients received placebo. The mean age was 14 years (range: 10 to

17 years), 56% were female, 85% White, 1% Black, 1% Asian, 13% Other, and 8% Hispanic. The mean LDL-C at baseline was 184 mg/dL; 17% of patients were on high-intensity statin, 62% on moderate-intensity statin, and 13% on ezetimibe.

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 24 was −38% (95% CI: −45%, −31%; p < 0.0001). For additional results, see Table 8 and Figure 6.

**Figure 6. Effect of REPATHA on LDL-C in Pediatric Patients with HeFH (Mean % Change from Baseline in HAUSER-RCT)**




EvoMab = evolocumab; LDL-C = low density lipoprotein cholesterol; QM = monthly (subcutaneous)
N = number of patients randomized and dosed in the full analysis set.
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

**Table 8. Effect of REPATHA on Lipid Parameters in Pediatric Patients with HeFH (Mean % Change from Baseline to Week 24 in HAUSER-RCT)**

| Treatment Group | LDL-C | Non-HDL-C | Apo B | Total Cholesterol |
|---|---|---|---|---|
| Placebo once monthly (n = 53) | -6 | -6 | -2 | -5 |
| REPATHA 420 mg once monthly (n = 104) | -44 | -41 | -35 | -32 |
| Mean difference from placebo (95% CI) | -38 (-45, -31) | -35 (-42, -28) | -32 (-39, -26) | -27 (-32, -21) |

All adjusted p-values < 0.0001.
n = number of patients randomized and dosed in the full analysis set.

Adults and Pediatric Patients with HoFH

Study 7 (TESLA, NCT01588496) was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with HoFH. In this trial, 33 patients received

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

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was −31% (95% CI: −44%, −18%; $p < 0.0001$). For additional results, see Table 9.

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

**Table 9. Effect of REPATHA on Lipid Parameters in Patients with HoFH (Mean % Change from Baseline to Week 12 in TESLA)**

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

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

Study 8 (TAUSSIG, NCT01624142) was a multicenter, open-label 5-year extension study with REPATHA in 106 patients with HoFH, who were treated with REPATHA as an adjunct to other lipid-lowering therapies. The study included 14 pediatric patients (ages 13 to 17 years). All patients in the study were initially treated with REPATHA 420 mg once monthly except for those receiving lipid apheresis at enrollment, who began with REPATHA 420 mg every 2 weeks. Dose frequency in non-apheresis patients could be titrated up to 420 mg once every 2 weeks based on LDL-C response and PCSK9 levels.

A total of 48 patients with HoFH received REPATHA 420 mg once monthly for at least 12 weeks in Study 8 followed by REPATHA 420 mg every 2 weeks for at least 12 weeks. Mean percent change from baseline in LDL-C were −20% at Week 12 of 420 mg once monthly treatment and −30% at Week 12 of 420 mg every 2 weeks treatment, based on available data.

Study 9 (HAUSER-OLE, NCT02624869) was an open-label, single-arm, multicenter, 80-week study to evaluate the safety, tolerability, and efficacy of REPATHA for LDL-C reduction in pediatric patients aged 10 to 17 years with HoFH *[see Use in Specific Populations (8.4)]*. Patients were on a low-fat diet and receiving background lipid-lowering therapy. Overall, 12 patients with HoFH received 420 mg REPATHA subcutaneously once monthly. The mean age was 12 years (range 11 to 17 years), 17% were female, 75% White, 17% Asian, and 8% Other. Median (Q1, Q3) LDL-C at baseline was 398 (343, 475) mg/dL, and all patients were on statins (atorvastatin or rosuvastatin) and ezetimibe. No patients were receiving lipid apheresis. The diagnosis of HoFH was made by genetic confirmation in all patients but enrollment by a clinical diagnosis was permitted. The median (Q1, Q3) percent change in LDL-C from baseline to Week 80 was −14% (−41, 4). Two of the 3 subjects with < 5% LDLR activity responded to evolocumab treatment.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

**Not Made with Natural Rubber Latex –**

| | | |
|---|---|---|
| 140 mg/mL prefilled single-dose SureClick® autoinjector | 2 pack | NDC 72511-393-02 |
| 140 mg/mL prefilled single-dose SureClick® autoinjector | 1 pack | NDC 72511-393-01 |
| 140 mg/mL prefilled single-dose Syringe | 1 pack | NDC 72511-501-01 |
| 420 mg/3.5 mL single-dose Pushtronex® system (on-body infusor with prefilled cartridge) | 1 pack | NDC 72511-770-01 |

**Contains Dry Natural Rubber –**

| | | |
|---|---|---|
| 140 mg/mL prefilled single-dose SureClick® autoinjector* | 2 pack | NDC 72511-760-02 |
| 140 mg/mL prefilled single-dose Syringe* | 1 pack | NDC 72511-750-01 |

* The needle cover of the glass prefilled single-dose SureClick® autoinjector and prefilled single-dose syringe contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex *[see Warnings and Precautions (5.1)]*.

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

For convenience, REPATHA may be kept at room temperature at 68°F to 77°F (20°C to 25°C) in the original carton for 30 days. If not used within the 30 days, discard REPATHA.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-Approved Patient Labeling (Patient Information and Instructions for Use).

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

Latex-Sensitivity
Instruct patients to inform their healthcare provider if they are sensitive to latex. Inform patients that REPATHA is available as prefilled single-dose SureClick® autoinjectors and prefilled single-dose syringes that either contain dry natural rubber (a derivative of latex) in the needle cover or are not made with natural rubber latex, and the carton and Instructions for Use state if the product contains dry natural rubber. Advise latex-sensitive patients that the needle cover of the glass prefilled single-dose SureClick® autoinjector and prefilled single-dose syringe that contain dry natural rubber (a derivative of latex) may cause allergic reactions in individuals sensitive to latex. *[see How Supplied/Storage and Handling (16)]*.

Pregnancy
Advise women who are exposed to REPATHA during pregnancy that there is a pregnancy safety study that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Amgen at 1-800-77-AMGEN (1-800-772-6436) or https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting *[see Use in Specific Populations (8.1)]*.

Administration

Provide guidance to patients and caregivers on proper subcutaneous administration technique and how to use the prefilled single-dose SureClick® autoinjector, prefilled single-dose syringe, or single-dose on-body infusor with prefilled cartridge correctly. Inform patients that it may take up to 15 seconds to administer REPATHA using the prefilled single-dose SureClick® autoinjector or prefilled single-dose syringe and about 5 minutes to administer REPATHA using the single-dose on-body infusor with prefilled cartridge.

The single-dose 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).

AMGEN

REPATHA® (evolocumab)

**Manufactured by:**
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License Number 1080
Patent: http://pat.amgen.com/repatha/

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

## What is REPATHA?

REPATHA is an injectable prescription medicine used:

- to reduce the risk of major adverse cardiovascular (CV) events, such as death from cardiovascular disease, heart attack, stroke, certain types of chest pain conditions (unstable angina) requiring hospitalization, or certain types of heart surgery, in adults at increased risk for these events.
- Along with diet and exercise to reduce low-density lipoprotein (LDL) or bad cholesterol in:
    - adults with high blood cholesterol levels called hypercholesterolemia.
    - adults and children aged 10 years and older with a type of high cholesterol called heterozygous familial hypercholesterolemia (HeFH).
    - adults and children aged 10 years and older with a type of high cholesterol called homozygous familial hypercholesterolemia (HoFH).

It is not known if REPATHA is safe and effective in children with HeFH or HoFH who are younger than 10 years of age or in children with other types of hypercholesterolemia.

## Who should not use REPATHA?

**Do not** use REPATHA if you or your child 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 or your child start using REPATHA, tell your healthcare provider about all your medical conditions, including if you or your child:

- are allergic to rubber or latex. REPATHA is available as prefilled single-dose SureClick® autoinjectors and prefilled single-dose syringes that either contain dry natural rubber (a derivative of latex) in the needle cover or are not made with natural rubber latex. The carton and "Instructions for Use" will state if your prefilled single-dose SureClick autoinjector or prefilled single-dose syringe contains dry natural rubber.
    - The single-dose 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.

If you or your child are pregnant or breastfeed during REPATHA treatment, you are encouraged to call Amgen at 1-800-772-6436 (1-800-77-AMGEN) or visit https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting to share information about the health of you and your baby or your child and your child's baby.

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

## How should I use REPATHA?

- **See the detailed "Instructions for Use" that comes with this Patient Information about the right way to prepare and give REPATHA.**
- Use REPATHA exactly as your healthcare provider tells you or your child to use it.
- REPATHA is given under the skin (subcutaneously), every 2 weeks or 1 time each month.
    - If you or your child have HoFH, the recommended starting dose is 420 mg one time each month. After 12 weeks, your healthcare provider may decide to increase the dose to 420 mg every two weeks. If you or your child receive lipid apheresis, your healthcare provider may decide to start you or your child on a dose of 420 mg every two weeks to match with the apheresis treatment and you or your child should take the dose after the apheresis treatment.
- REPATHA comes as a prefilled single-dose (1 time) autoinjector (SureClick autoinjector), as a prefilled single-dose syringe or as a single-dose Pushtronex system (on-body infusor with prefilled cartridge). Your healthcare provider will prescribe the type and dose that is best for you or your child.

- If your healthcare provider prescribes you or your child the 420 mg dose, you or your child may use:
    - a single-dose on-body infusor with prefilled cartridge to give the injection over 5 minutes, or
    - 3 separate injections in a row, using a different prefilled single-dose SureClick autoinjector or prefilled single-dose syringe for each injection. Give all of these injections within 30 minutes.
- If your healthcare provider decides that you or your child or a caregiver can give REPATHA, you or your child or your caregiver should receive training on the right way to prepare and inject REPATHA. **Do not** try to inject REPATHA until you or your child have been shown the right way by your healthcare provider or nurse.
    - If you or your child are using the prefilled single-dose SureClick autoinjector, put the **yellow safety guard (needle inside) of the prefilled single-dose SureClick autoinjector on the skin before injecting.**
- You or your child can inject into the thigh, upper arm, or stomach (abdomen), except for a **two**-inch area around the belly button.
- **Do not** choose an area where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.
- Always check the label of your prefilled single-dose SureClick autoinjector, prefilled single-dose syringe, or single-dose on-body infusor with prefilled cartridge to make sure you have the correct medicine and the correct dose of REPATHA before each injection.
- If you or your child forget to use REPATHA or are not able to take the dose at the regular time, inject your or your child's missed dose as soon as you remember, as long as it is within 7 days of the missed dose.
    - If it is more than 7 days from the missed dose and you or your child are using the every-2-week dose, inject the next dose based on the original schedule. This will put you or your child back on the original schedule.
    - If it is more than 7 days from the missed dose and you or your child are using the 1 time each-month dose, inject the dose and start a new schedule using this date.

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

- If your healthcare provider has prescribed REPATHA along with other cholesterol-lowering medicines for you or your child, follow instructions from your healthcare provider. Read the Patient Information for those medicines.
- If you or your child 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 or your child stop using REPATHA, the cholesterol levels can increase.

**What are the possible side effects of REPATHA?**

REPATHA can cause serious side effects including:

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

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

Tell your healthcare provider if you or your child 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.

**How should I store REPATHA?**

- Store REPATHA in the refrigerator between 36°F to 46°F (2°C to 8°C). Store REPATHA in the original carton until use to protect it from light.
- If needed, REPATHA can be stored at room temperature between 68°F to 77°F (20°C to 25°C) in the original carton for up to 30 days. Throw away REPATHA that has been stored at room temperature for more than 30 days.
- Do not freeze REPATHA.
- Do not shake REPATHA.

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

**General information about the safe and effective use of REPATHA.**

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

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

**What are the ingredients in REPATHA?**

- Active Ingredient: evolocumab
- Inactive Ingredients: proline; acetate; polysorbate 80; water for injection, USP; 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/

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 08/2025

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# INSTRUCTIONS FOR USE

**REPATHA® [ri-PAth-a]**
**(evolocumab)**
**injection, for subcutaneous use**
**140 mg/mL**
**prefilled single-dose SureClick® autoinjector**

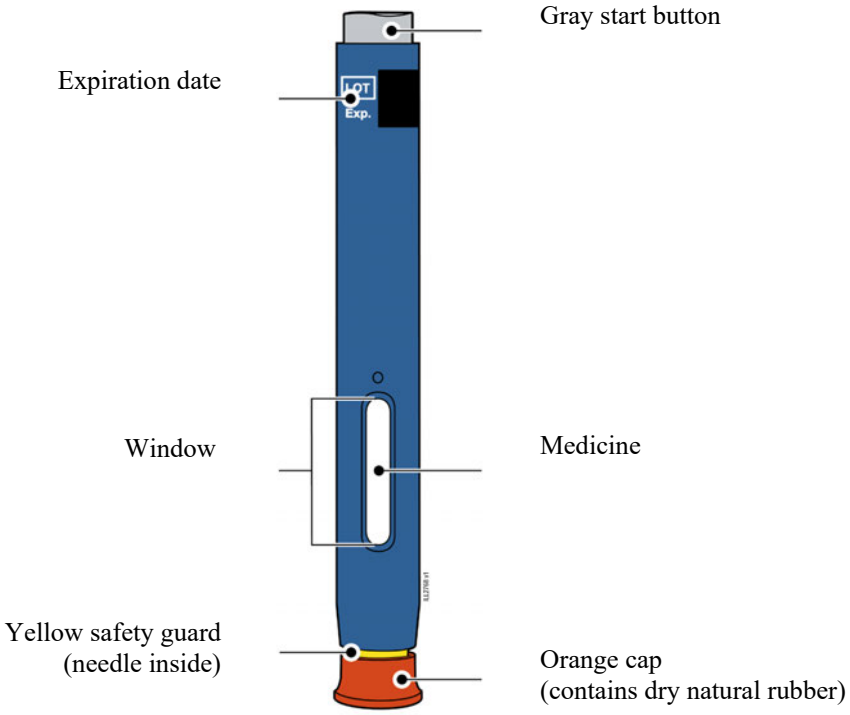
**(contains dry natural rubber)**

This Instructions for Use contains information on how to inject REPATHA with a SureClick autoinjector.

If your healthcare provider decides that you or a caregiver may be able to give your injections of REPATHA at home, you should receive training on the right way to prepare and inject REPATHA. Do not try to inject yourself until you have been shown the right way to give the injections by your healthcare provider or nurse.

The medicine in the REPATHA autoinjector is for injection under the skin (subcutaneous injection). See the REPATHA Patient Information for information about REPATHA.

## Getting to know the prefilled autoinjector



## Important Information You Need to Know Before Injecting REPATHA

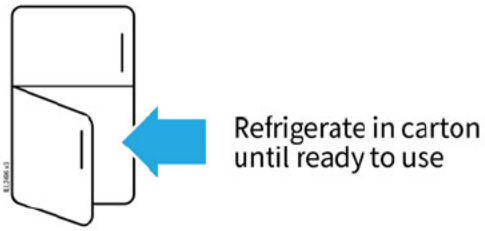
- It is important that you do not try to give the injection until you have fully read and understood this Instructions for Use.
- **The orange cap on the REPATHA SureClick autoinjector contains a yellow safety guard (located inside the cap) that contains dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.**
- Check the autoinjector label and prescription to make sure you have the correct medicine and dose.
- **Do not** use the autoinjector if the carton is damaged or the seal is broken.
- **Do not** use the autoinjector after the expiration date on the label.
- **Do not** shake the autoinjector.
- **Do not** remove the orange cap from the autoinjector until you are ready to inject.
- **Do not** use the autoinjector if it has been frozen.
- **Do not** use the autoinjector if it has been dropped on a hard surface. Part of the autoinjector may be broken even if you cannot see the break. Use a new autoinjector, and call 1-844-REPATHA (1-844-737-2842).

**Frequently asked questions:**
For additional information and answers to frequently asked questions, visit **www.repatha.com**.

**Where to get help:**
If you want more information or help using REPATHA:

- Contact your healthcare provider,
- Visit **www.repatha.com**, or
- Call 1-844-REPATHA (1-844-737-2842).

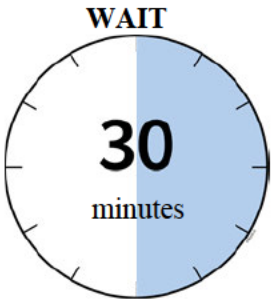
## Storing and Preparing to Inject REPATHA




**1 Refrigerate the autoinjector carton until you are ready to use it.**

- Keep the autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep the autoinjector in the original carton to protect it from light or physical damage.
- **Do not** freeze the autoinjector.
- **Do not** store the autoinjector in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.

**Important:** Keep the autoinjector and all medicines out of the sight and reach of children.



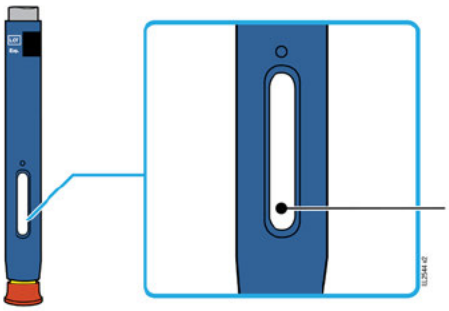

**2** **Wait 30 minutes for the autoinjector to reach room temperature.**

- Remove the number of autoinjectors you need for your injection and put any unused autoinjectors back into the refrigerator.
- Let the autoinjector warm up naturally.
- **Do not** heat the autoinjector with hot water, a microwave, or direct sunlight.
- **Do not** shake the autoinjector at any time.
- Using the autoinjector at room temperature makes sure the full dose is delivered and allows for a more comfortable injection.


**3** **You may keep REPATHA at room temperature for up to 30 days, if needed.**

- For example, when you are traveling, you may keep REPATHA at room temperature.
  - Keep it at room temperature between 68°F to 77°F (20°C to 25°C).
  - Record the date you removed it from the refrigerator and use it within **30** days.

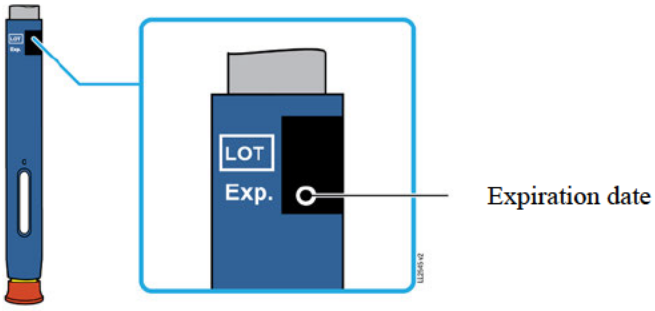
**Important:** Place the autoinjector in a sharps disposal container if it has reached room temperature and has not been used within **30** days.




**4** **Inspect the medicine. It should be clear and colorless to slightly yellow.**

- It is okay to see air bubbles.
- **Do not** use the autoinjector if the medicine is cloudy, discolored, or contains flakes or particles.

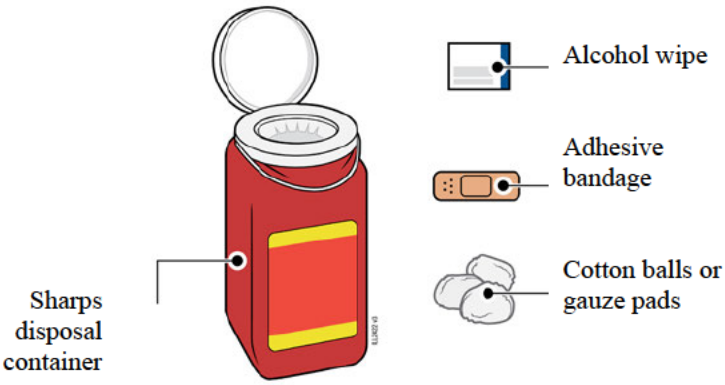
**Important:** If the medicine is cloudy, discolored, or contains flakes or particles, or if the autoinjector is damaged or expired, call 1-844-REPATHA (1-844-737-2842).




**5** **Check the expiration date (Exp.) and inspect the autoinjector for damage.**

- **Do not** use the autoinjector if the expiration date has passed.
- **Do not** use the autoinjector if:
  - the orange cap is missing or loose in carton,
  - it has cracks or broken parts, or
  - it has been dropped on a hard surface.

## Getting Ready to Inject REPATHA




**6 Gather and place the following items for your injection on a clean, flat, and well-lit surface:**

- REPATHA autoinjector (room temperature),
- Sharps disposal container [see Completing the Injection and Disposal],
- Alcohol wipe,
- Adhesive bandage, and
- Cotton balls or gauze pads.

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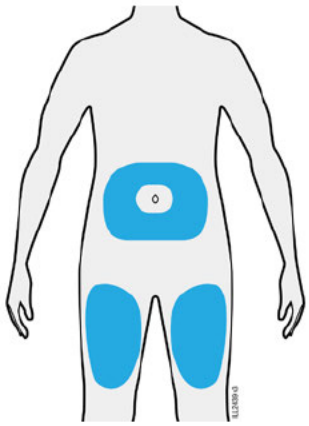

**7 Select 1 of these injection sites.**

- Select the thigh or stomach (except for 2 inches around the belly button).
- Someone else can inject in your thigh, stomach, or back of your upper arm.
- Change injection site each time, shifting the area of the injection to avoid skin irritation.

**Important:** Avoid areas with scars or stretch marks, or where the skin is tender, bruised, red, hard, raised, thick or scaly skin patch, or lesion.

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**8** **Wash your hands thoroughly with soap and water.**

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**9** **Clean the injection site with an alcohol wipe.**

- Let the skin dry on its own.
- **Do not** touch this area again before injecting.

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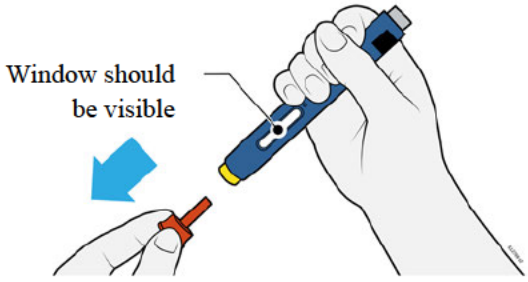
## Injecting REPATHA

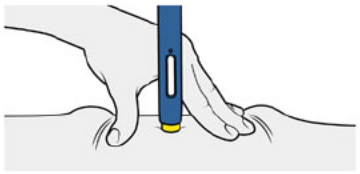
**Important:** Only remove the orange cap when you can inject right away (within 5 minutes) because the medicine can dry out. **Do not** recap.




**10** **Grasp the autoinjector so you can see the window. Pull the orange cap straight off. You may need to pull hard.**

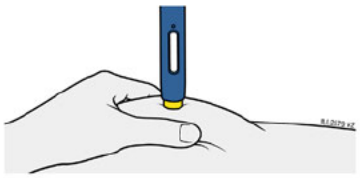
- **Do not** twist, bend, or wiggle the orange cap to pull it off.
- **Never** put the orange cap back on. It may damage the needle.
- **Do not** put your finger inside the yellow safety guard.
- It is normal to see a drop of medicine come out of the needle or yellow safety guard.

**STRETCH**



OR

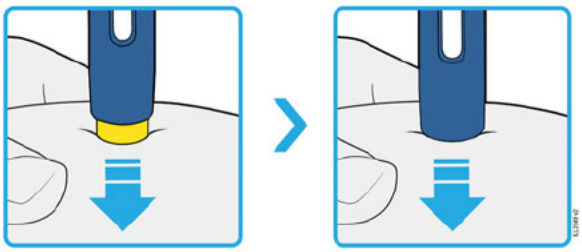
**PINCH**



**11** **Stretch or pinch the skin to create a firm surface at the injection site until the injection is finished. Place the yellow safety guard straight against the skin.**

- Make sure you can see the window.
- Make sure the autoinjector is positioned straight on the injection site (at a 90-degree angle).

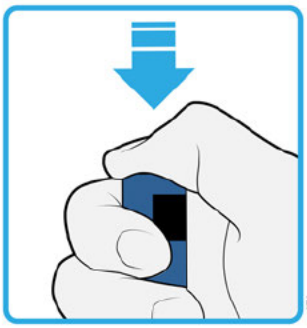
**PUSH**
**and hold against skin**



**12** **Firmly push the autoinjector down until the yellow safety guard stops moving. Hold the autoinjector down, do not lift.**

- The yellow safety guard pushes in and unlocks the gray start button.

**PRESS**
**gray start button**

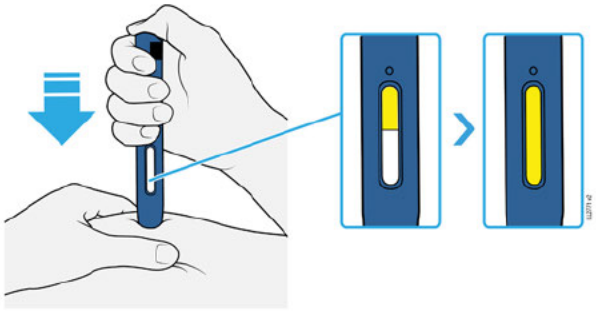


**13** **Keep pushing the autoinjector down and press the gray start button to start the injection.**

- You may hear or feel a click.
- The window starts to turn yellow.
- It is okay to let go of the gray start button.

---

**WATCH**
**window will turn fully yellow**

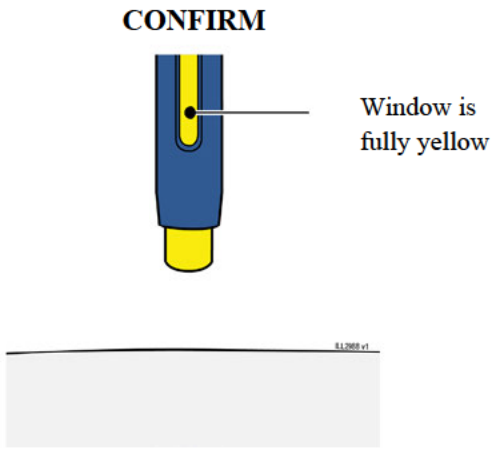


**14** **Keep pushing the autoinjector down. Wait for the window to turn fully yellow.**

- The injection may take up to **15** seconds to complete.
- You may hear or feel a click.
- After the window turns fully yellow, lift the autoinjector away from the skin.
- The yellow safety guard locks around the needle.

---

## Completing the Injection and Disposal

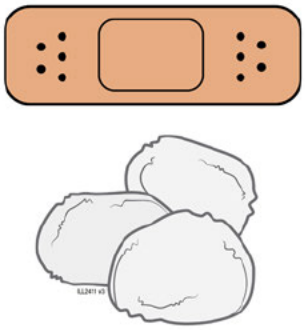



**15** **Confirm a full dose of medicine was injected.**

- **Do not** touch the yellow safety guard.
- A small drop of liquid on the injection site is okay.

**Important:** If the window has not turned fully yellow, or if it looks like the medicine is still coming out, a full dose was not injected. Call your healthcare provider right away.

---



**16** **Check the injection site.**

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

---

**17** **Place the used autoinjector and orange cap in an FDA-cleared sharps disposal container.**

**Important:** Do not throw away the autoinjector in your household trash.

- **Do not** reuse the autoinjector.
- **Do not** touch the yellow safety guard.

---

**Additional information about your sharps disposal container**
**If you do not have an 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.

**Disposing of sharps disposal containers:**
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.

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

**For more information or help call 1-844-REPATHA (1-844-737-2842).**

**REPATHA (evolocumab)**

AMGEN

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License Number 1080


1XXXXXX
This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: 08/2025
vxx

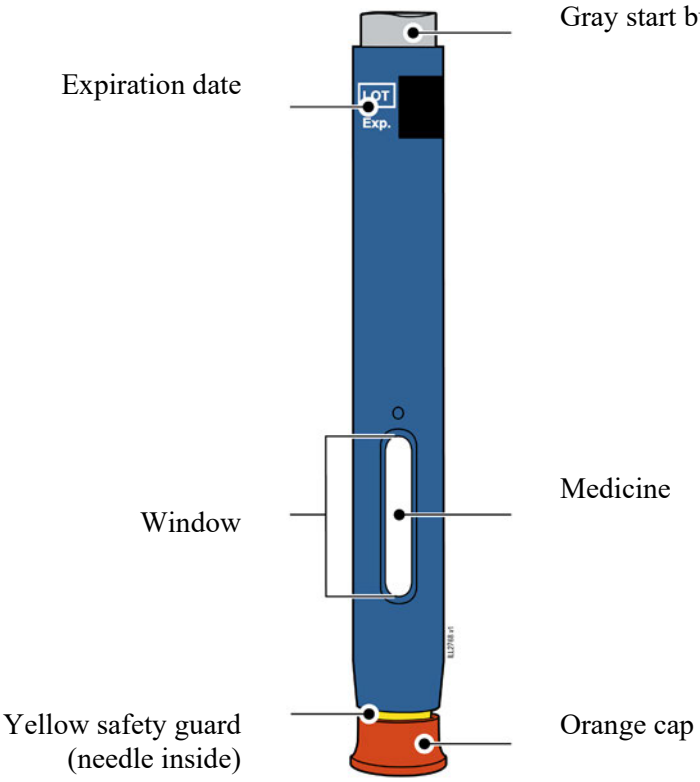
**INSTRUCTIONS FOR USE**
**REPATHA® [ri-PAth-a]**
**(evolocumab)**
**injection, for subcutaneous use**
**140 mg/mL**
**prefilled single-dose SureClick® autoinjector**

This Instructions for Use contains information on how to inject REPATHA with a SureClick autoinjector.

If your healthcare provider decides that you or a caregiver may be able to give your injections of REPATHA at home, you should receive training on the right way to prepare and inject REPATHA. Do not try to inject yourself until you have been shown the right way to give the injections by your healthcare provider or nurse.

The medicine in the REPATHA autoinjector is for injection under the skin (subcutaneous injection). See the REPATHA Patient Information for information about REPATHA.

## Getting to know the prefilled autoinjector



## Important Information You Need to Know Before Injecting REPATHA

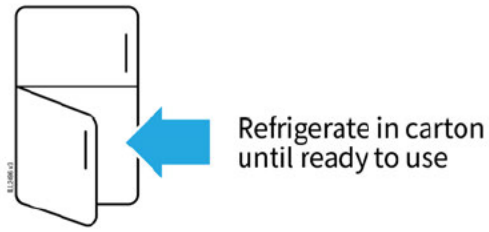
- It is important that you do not try to give the injection until you have fully read and understood this Instructions for Use.
- Check the autoinjector label and prescription to make sure you have the correct medicine and dose.
- **Do not** use the autoinjector if the carton is damaged or the seal is broken.
- **Do not** use the autoinjector after the expiration date on the label.
- **Do not** shake the autoinjector.
- **Do not** remove the orange cap from the autoinjector until you are ready to inject.
- **Do not** use the autoinjector if it has been frozen.
- **Do not** use the autoinjector if it has been dropped on a hard surface. Part of the autoinjector may be broken even if you cannot see the break. Use a new autoinjector, and call 1-844-REPATHA (1-844-737-2842).
- The autoinjector is not made with natural rubber latex.

**Frequently asked questions:**
For additional information and answers to frequently asked questions, visit **www.repatha.com**.

**Where to get help:**
If you want more information or help using REPATHA:

- Contact your healthcare provider,
- Visit **www.repatha.com**, or
- Call 1-844-REPATHA (1-844-737-2842).

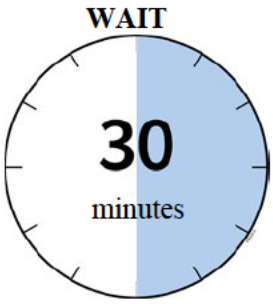
## Storing and Preparing to Inject REPATHA




**1 Refrigerate the autoinjector carton until you are ready to use it.**

- Keep the autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep the autoinjector in the original carton to protect it from light or physical damage.
- **Do not** freeze the autoinjector.
- **Do not** store the autoinjector in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.

**Important:** Keep the autoinjector and all medicines out of the sight and reach of children.



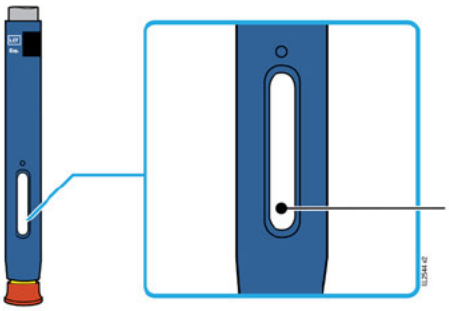

**2** **Wait 30 minutes for the autoinjector to reach room temperature.**

- Remove the number of autoinjectors you need for your injection and put any unused autoinjectors back into the refrigerator.
- Let the autoinjector warm up naturally.
- **Do not** heat the autoinjector with hot water, a microwave, or direct sunlight.
- **Do not** shake the autoinjector at any time.
- Using the autoinjector at room temperature makes sure the full dose is delivered and allows for a more comfortable injection.


**3** **You may keep REPATHA at room temperature for up to 30 days, if needed.**

- For example, when you are traveling, you may keep REPATHA at room temperature.
  - Keep it at room temperature between 68°F to 77°F (20°C to 25°C).
  - Record the date you removed it from the refrigerator and use it within **30** days.

**Important:** Place the autoinjector in a sharps disposal container if it has reached room temperature and has not been used within **30** days.

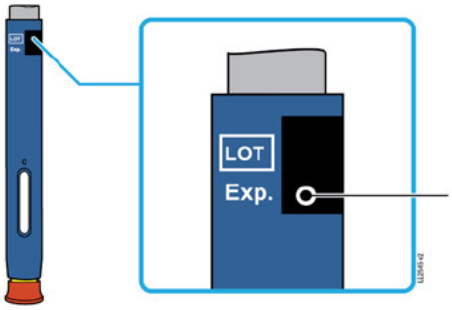


Medicine

**4** **Inspect the medicine. It should be clear and colorless to slightly yellow.**

- It is okay to see air bubbles.
- **Do not** use the autoinjector if the medicine is cloudy, discolored, or contains flakes or particles.

**Important:** If the medicine is cloudy, discolored, or contains flakes or particles, or if the autoinjector is damaged or expired, call 1-844-REPATHA (1-844-737-2842).

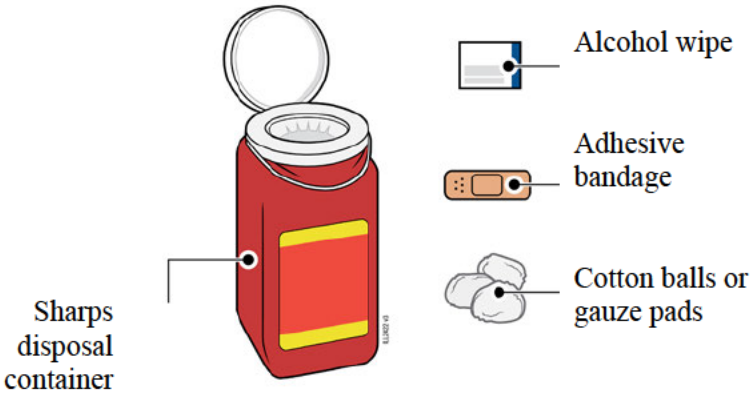



Expiration date

**5** **Check the expiration date (Exp.) and inspect the autoinjector for damage.**

- **Do not** use the autoinjector if the expiration date has passed.
- **Do not** use the autoinjector if:
  - the orange cap is missing or loose in carton,
  - it has cracks or broken parts, or
  - it has been dropped on a hard surface.

## Getting Ready to Inject REPATHA




**6** **Gather and place the following items for your injection on a clean, flat, and well-lit surface:**

- REPATHA autoinjector (room temperature),
- Sharps disposal container [see Completing the Injection and Disposal],
- Alcohol wipe,
- Adhesive bandage, and
- Cotton balls or gauze pads.

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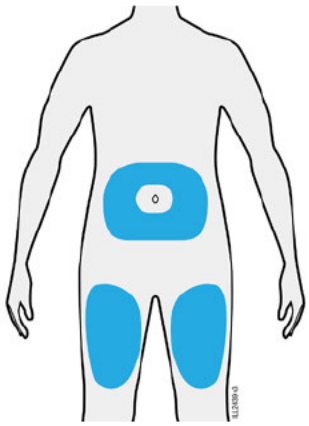


**7** **Select 1 of these injection sites.**

- Select the thigh or stomach (except for 2 inches around the belly button).
- Someone else can inject in your thigh, stomach, or back of your upper arm.
- Change injection site each time, shifting the area of the injection to avoid skin irritation.

**Important:** Avoid areas with scars or stretch marks, or where the skin is tender, bruised, red, hard, raised, thick or scaly skin patch, or lesion.

---

**8** **Wash your hands thoroughly with soap and water.**

---

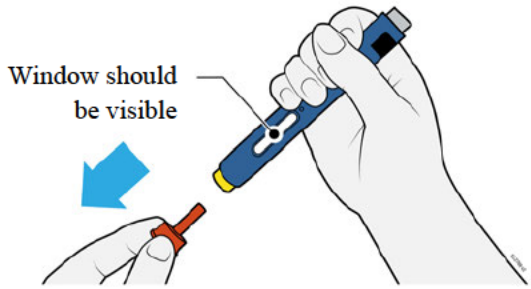
**9** **Clean the injection site with an alcohol wipe.**

- Let the skin dry on its own.
- **Do not** touch this area again before injecting.

---

## Injecting REPATHA

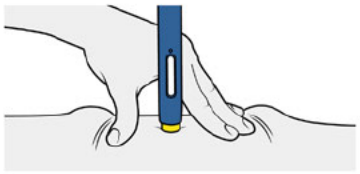
**Important:** Only remove the orange cap when you can inject right away (within 5 minutes) because the medicine can dry out. **Do not** recap.




**10** **Grasp the autoinjector so you can see the window. Pull the orange cap straight off. You may need to pull hard.**

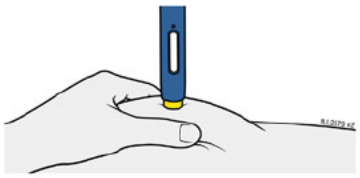
- **Do not** twist, bend, or wiggle the orange cap to pull it off.
- **Never** put the orange cap back on. It may damage the needle.
- **Do not** put your finger inside the yellow safety guard.
- It is normal to see a drop of medicine come out of the needle or yellow safety guard.

**STRETCH**



**OR**

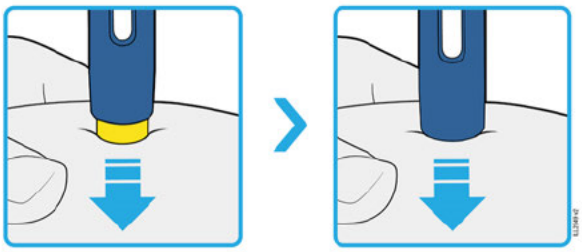
**PINCH**



**11** **Stretch or pinch the skin to create a firm surface at the injection site until the injection is finished. Place the yellow safety guard straight against the skin.**

- Make sure you can see the window.
- Make sure the autoinjector is positioned straight on the injection site (at a 90-degree angle).

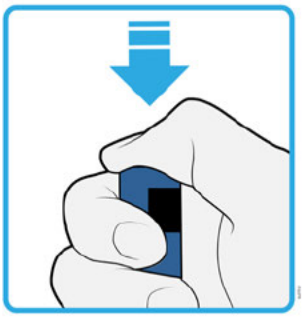
**PUSH**
**and hold against skin**



**12** **Firmly push the autoinjector down until the yellow safety guard stops moving. Hold the autoinjector down, do not lift.**

- The yellow safety guard pushes in and unlocks the gray start button.

**PRESS**
**gray start button**

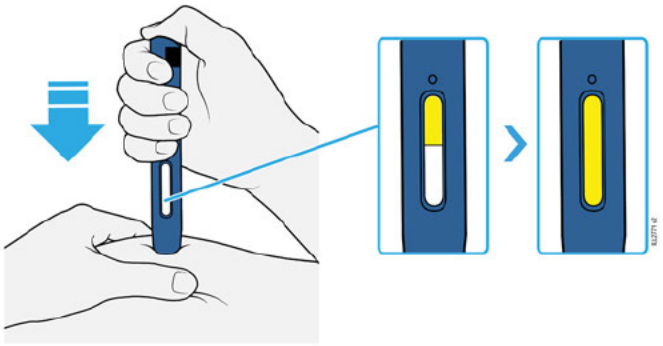


**13** **Keep pushing the autoinjector down and press the gray start button to start the injection.**

- You may hear or feel a click.
- The window starts to turn yellow.
- It is okay to let go of the gray start button.

---

**WATCH**
**window will turn fully yellow**



**14** **Keep pushing the autoinjector down. Wait for the window to turn fully yellow.**

- The injection may take up to **15** seconds to complete.
- You may hear or feel a click.
- After the window turns fully yellow, lift the autoinjector away from the skin.
- The yellow safety guard locks around the needle.

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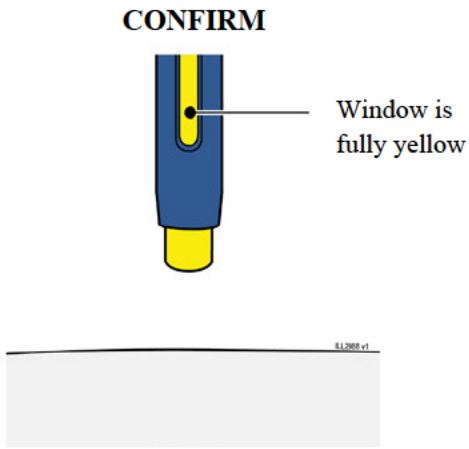
## Completing the Injection and Disposal




**15** **Confirm a full dose of medicine was injected.**

- **Do not** touch the yellow safety guard.
- A small drop of liquid on the injection site is okay.

**Important:** If the window has not turned fully yellow, or if it looks like the medicine is still coming out, a full dose was not injected. Call your healthcare provider right away.

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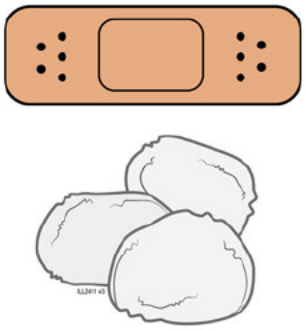


**16** **Check the injection site.**

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

---

**17 Place the used autoinjector and orange cap in an FDA-cleared sharps disposal container.**

**Important:** Do not throw away the autoinjector in your household trash.

- **Do not** reuse the autoinjector.
- **Do not** touch the yellow safety guard.

---

**Additional information about your sharps disposal container**
**If you do not have an 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.

**Disposing of sharps disposal containers:**
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.

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

**For more information or help call 1-844-REPATHA (1-844-737-2842).**

**REPATHA (evolocumab)**

AMGEN

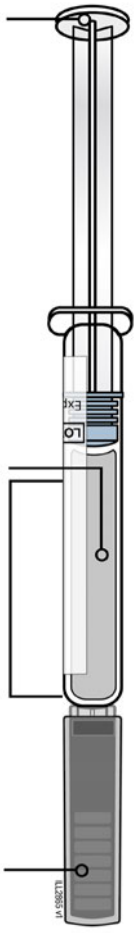
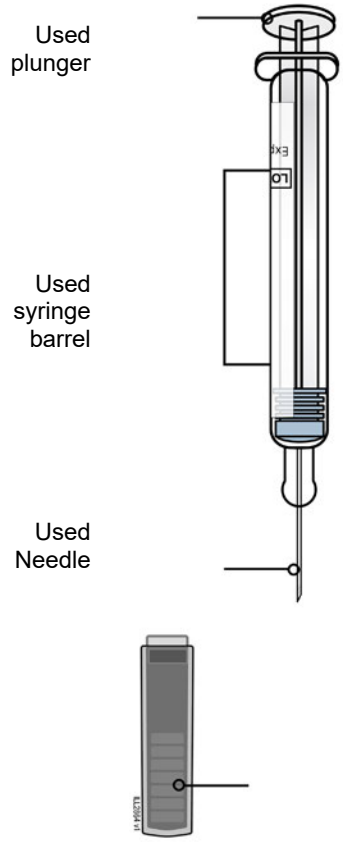
Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License Number 1080


1XXXXXX
This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: 08/2025
vxx

**Instructions for Use**
**Repatha® (ri-PAth-a)**
**(evolocumab)**
**prefilled single-dose syringe**

**(contains dry natural rubber)**

**Getting to know the prefilled syringe**

| Before use | After use |
|---|---|
|  |  |
| Needle is inside | |

**Important**

**Before you use a prefilled single-dose syringe, read this important information:**

- It is important that you **do not** try to give the injection until you have fully read and understood this Instructions for Use.
- Check the carton, prefilled syringe label, and prescription to make sure you have the correct medicine and dose.
- Check the expiration date on the REPATHA prefilled syringe carton: **do not** use if this date has passed.
- 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 gray needle cap on the prefilled syringe contains dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.**

**Storage of REPATHA:**

- Keep the prefilled syringe in the original carton to protect from light during storage.
- Keep the prefilled syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If removed from the refrigerator, the prefilled syringe 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. Place the prefilled syringe in a sharps disposal container if it has reached room temperature and has not been used within 30 days.
- **Do not** freeze the prefilled syringe or use a prefilled syringe that has been frozen.
- **Do not** store the prefilled syringe in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.

**Do not**:

- **Do not** use the prefilled syringe if the packaging is open or damaged.
- **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.
- **Do not** use the prefilled syringe if it has been dropped onto a hard surface. Part of the prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe and call 1-844-REPATHA (1-844-737-2842).
- **Do not** use the prefilled syringe after the expiration date.

A healthcare provider who knows how to use the prefilled syringe 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 prefilled syringe and all medicines out of the sight and reach of children.

**Step 1: Prepare**

| | |
|---|---|
| **1 A** | Remove the prefilled syringe carton from the refrigerator and wait 30 minutes. |

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


Using the prefilled syringe at room temperature makes sure the full dose is delivered and allows for a more comfortable injection. **Do not** heat the syringe. Let it warm up on its own naturally.

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

**Do not** leave the prefilled syringe in direct sunlight.

**Do not** shake the prefilled syringe.

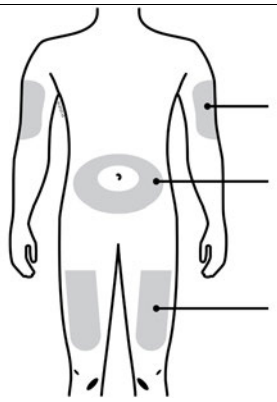
| 1 B | Gather all materials needed for your injection. |
|---|---|

Wash your hands thoroughly with soap and water.

**On a clean, well-lit, flat work surface, place:**

- 1 REPATHA prefilled syringe in carton
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container (see Step 4: Finish)

| 1 C | Choose your injection site. |
|---|---|




**You can use the:**

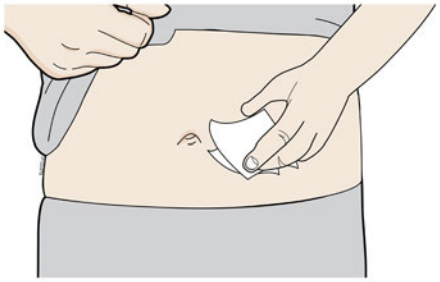
- front of your thigh
- stomach (abdomen), except for a **2** inch area around your belly button

**If someone else is giving you the injection, they can also use the outer area of the upper arm.**

**Do not** choose an area where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

Choose a different site each time you give yourself an injection.

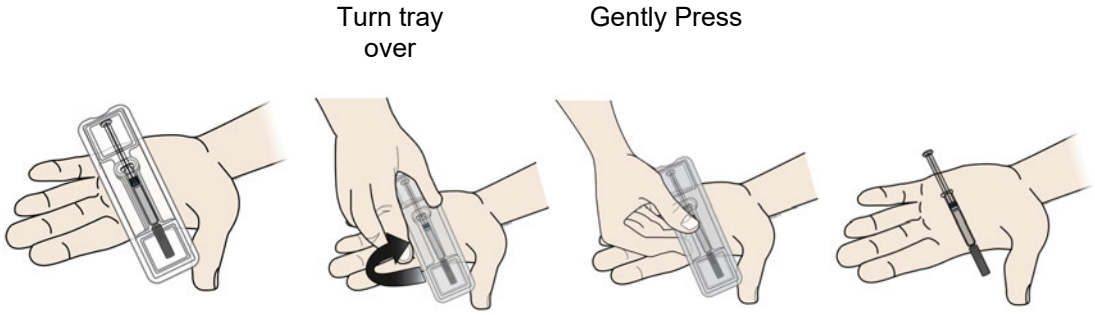
| **1 D** | Clean your injection site. |
|---|---|



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

**Do not** touch this area of skin again before injecting.

| **1 E** | Remove prefilled syringe from tray. |
|---|---|




To remove:

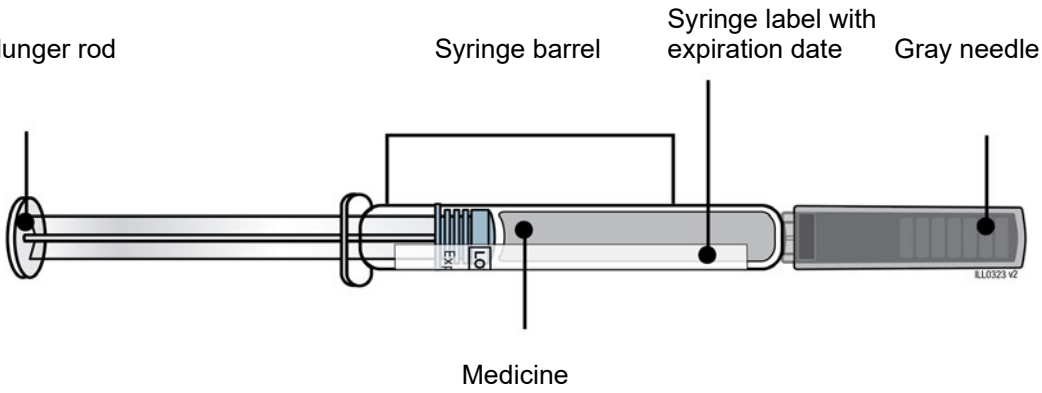
- Peel paper off of tray.
- Place the tray on your hand.
- Turn the tray over and gently press the middle of the tray's back to release the prefilled syringe into your palm.
- If the prefilled syringe does not release from the tray, gently press on the back of the tray.

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

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

Always hold the prefilled syringe by the syringe barrel.

| 1 F | Check the medicine and syringe. |
|---|---|




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

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

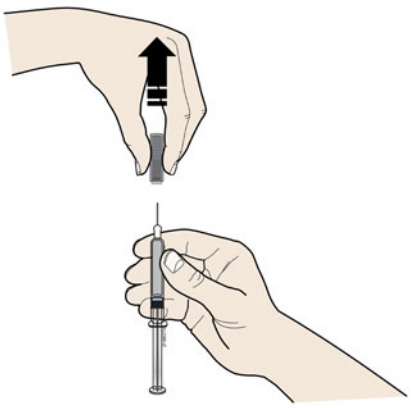
**Do not** use the prefilled syringe if any part of the prefilled syringe appears cracked or broken.

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

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

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

| Step 2: Get ready | |
|---|---|
| 2 A | Carefully pull the gray needle cap straight out and away from your body. **Do not** leave the gray needle cap off for more than **5 minutes.** This can dry out the medicine. |



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

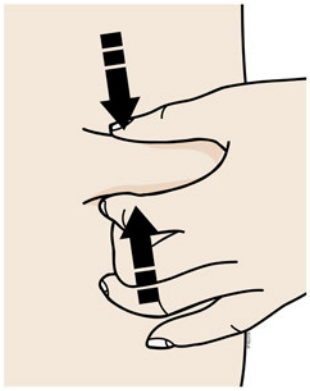
Place the gray needle cap in the sharps disposal container right away.

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

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

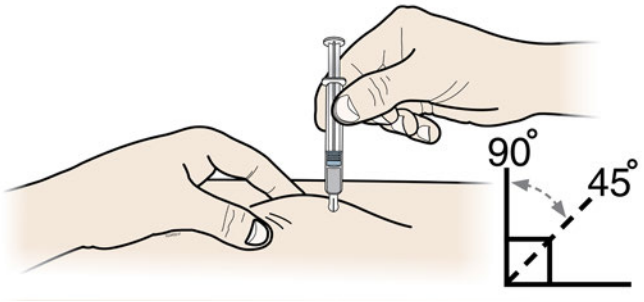
**Do not** try to remove any air bubbles in the syringe before the injection.

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



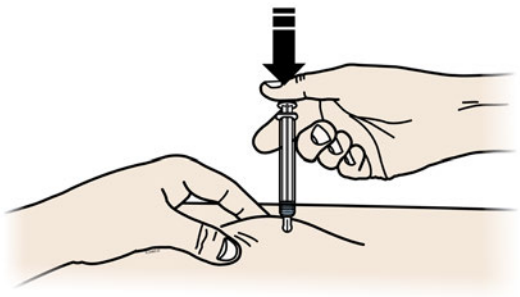
Pinch the skin firmly between your thumb and fingers, creating an area about 2 inches wide.
It is important to keep the skin pinched while injecting.

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

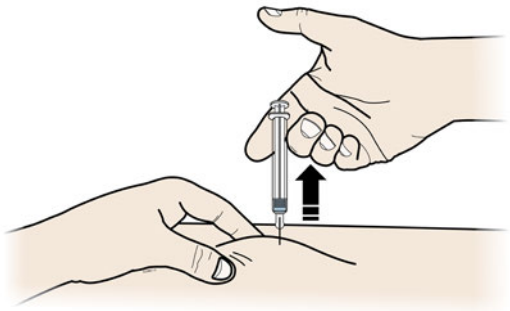



**Do not** place your finger on the plunger rod while inserting the needle.

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



| | |
|---|---|
| **3 C** | When the prefilled syringe is empty, **release** your thumb, and gently lift the syringe out of the skin. |



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

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

**Do not** reuse the used prefilled syringe.

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

- Put the used prefilled syringe in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the syringe in your household trash.
- If you do not have an 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.

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

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

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

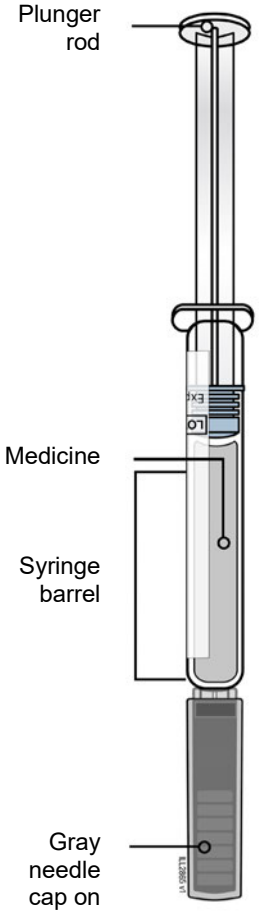
Manufactured by:
Amgen Inc.
Thousand Oaks, CA 91320-1799
U.S. License Number 1080

<part number> Revised: 11/2024 v4

**Instructions for Use**
**Repatha® (ri-PAth-a)**
**(evolocumab)**
**prefilled single-dose syringe**

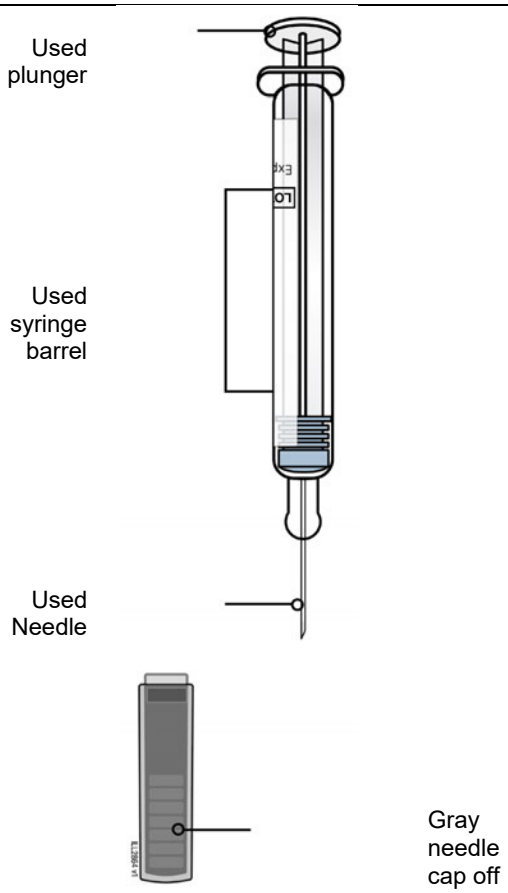
## Getting to know the prefilled syringe

### Before use




Needle is inside

### After use



**Important**

**Before you use a prefilled single-dose syringe, read this important information:**

- It is important that you **do not** try to give the injection until you have fully read and understood this Instructions for Use.
- Check the carton, prefilled syringe label, and prescription to make sure you have the correct medicine and dose.
- Check the expiration date on the REPATHA prefilled syringe carton: **do not** use if this date has passed.
- 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 prefilled syringe is not made with natural rubber latex.

**Storage of REPATHA:**

- Keep the prefilled syringe in the original carton to protect from light during storage.
- Keep the prefilled syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If removed from the refrigerator, the prefilled syringe 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. Place the prefilled syringe in a sharps disposal container if it has reached room temperature and has not been used within 30 days.
- **Do not** freeze the prefilled syringe or use a prefilled syringe that has been frozen.
- **Do not** store the prefilled syringe in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.

**Do not**:

- **Do not** use the prefilled syringe if the packaging is open or damaged.
- **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.
- **Do not** use the prefilled syringe if it has been dropped onto a hard surface. Part of the prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe and call 1-844-REPATHA (1-844-737-2842).
- **Do not** use the prefilled syringe after the expiration date.

A healthcare provider who knows how to use the prefilled syringe 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 prefilled syringe and all medicines out of the sight and reach of children.

**Step 1: Prepare**

| | |
|---|---|
| **1 A** | Remove the prefilled syringe carton from the refrigerator and wait 30 minutes. |

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


Using the prefilled syringe at room temperature makes sure the full dose is delivered and allows for a more comfortable injection. **Do not** heat the syringe. Let it warm up on its own naturally.

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

**Do not** leave the prefilled syringe in direct sunlight.

**Do not** shake the prefilled syringe.

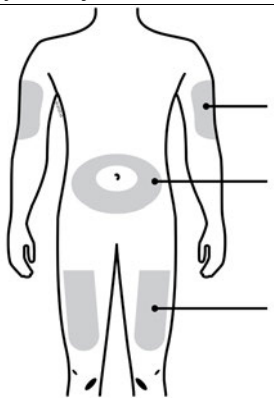
| **1 B** | Gather all materials needed for your injection. |
|---|---|

Wash your hands thoroughly with soap and water.

**On a clean, well-lit, flat work surface, place:**

- 1 REPATHA prefilled syringe in carton
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container (see Step 4: Finish)

| **1 C** | Choose your injection site. |
|---|---|




**You can use the:**

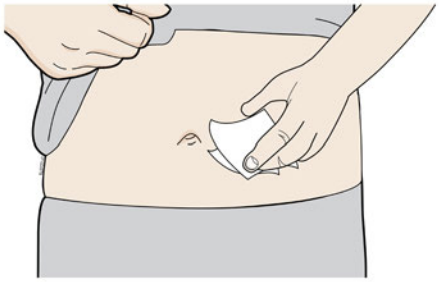
- front of your thigh
- stomach (abdomen), except for a **2** inch area around your belly button

**If someone else is giving you the injection, they can also use the outer area of the upper arm.**

**Do not** choose an area where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

Choose a different site each time you give yourself an injection.

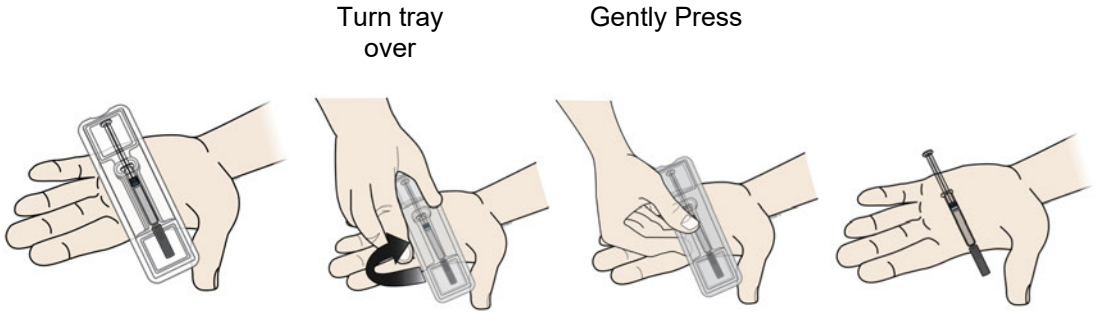
| **1 D** | Clean your injection site. |
|---|---|



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

**Do not** touch this area of skin again before injecting.

| **1 E** | Remove prefilled syringe from tray. |
|---|---|




To remove:

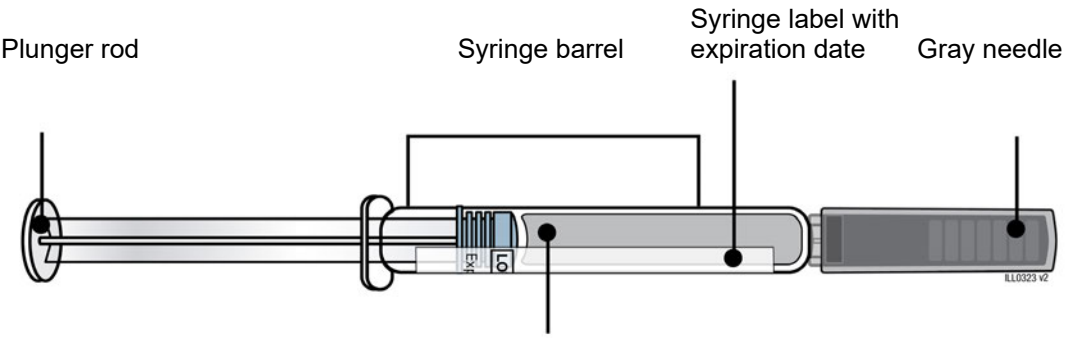
- Peel paper off of tray.
- Place the tray on your hand.
- Turn the tray over and gently press the middle of the tray's back to release the prefilled syringe into your palm.
- If the prefilled syringe does not release from the tray, gently press on the back of the tray.

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

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

Always hold the prefilled syringe by the syringe barrel.

| | |
|---|---|
| **1 F** | Check the medicine and syringe. |




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

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

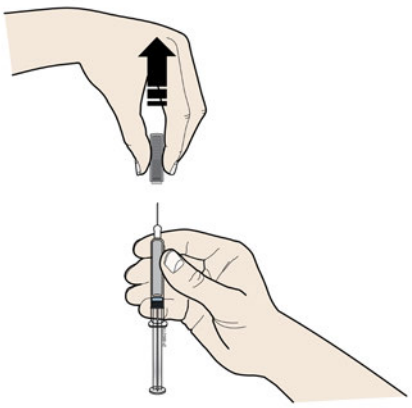
**Do not** use the prefilled syringe if any part of the prefilled syringe appears cracked or broken.

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

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

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

| **Step 2: Get ready** | |
|---|---|
| **2 A** | Carefully pull the gray needle cap straight out and away from your body. **Do not** leave the gray needle cap off for more than **5 minutes.** This can dry out the medicine. |



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

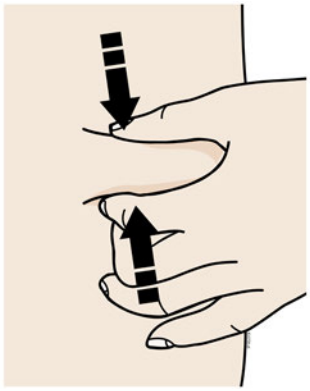
Place the gray needle cap in the sharps disposal container right away.

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

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

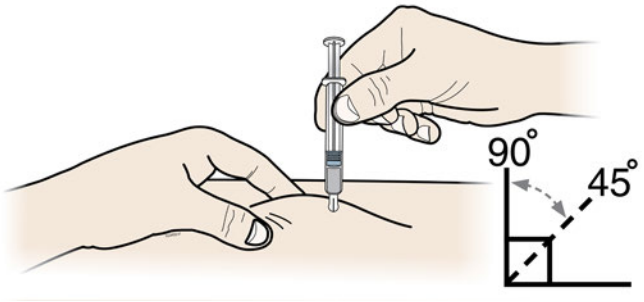
**Do not** try to remove any air bubbles in the syringe before the injection.

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



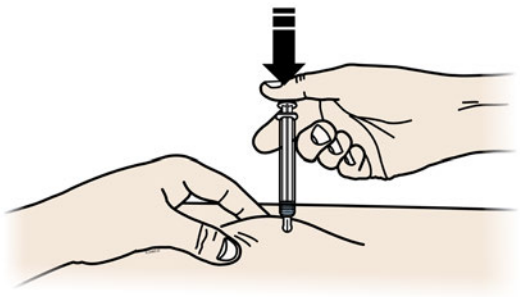
Pinch the skin firmly between your thumb and fingers, creating an area about 2 inches wide.
It is important to keep the skin pinched while injecting.

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

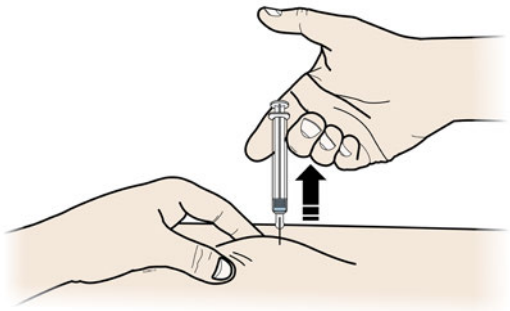



**Do not** place your finger on the plunger rod while inserting the needle.

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

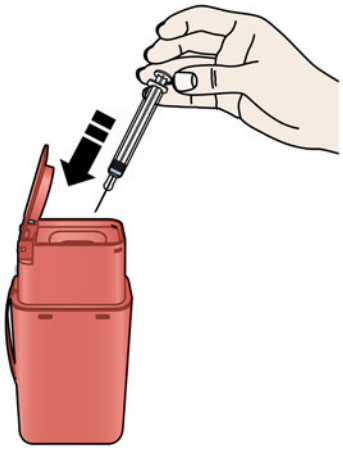


| | |
|---|---|
| **3 C** | When the prefilled syringe is empty, **release** your thumb, and gently lift the syringe out of the skin. |



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

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



**Do not** reuse the used prefilled syringe.

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

- Put the used prefilled syringe in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the syringe in your household trash.
- If you do not have an 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.

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

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

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

Manufactured by:
Amgen Inc.
Thousand Oaks, CA 91320-1799
U.S. License Number 1080

<part number> Issued: 11/2024 v1

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125522Orig1s045

# CLINICAL REVIEW(S)

# Prior Approval Labeling Supplement-Clinical Memo

| | |
|---|---|
| **BLA:** | 125522/SD2605/S-45 |
| **Applicant:** | Amgen |
| **Drug name:** | Repatha/evolocumab |
| **Date of submission:** | December 19, 2024 |
| **Type of submission:** | Prior Approval Supplement #45 |
| **Review Division:** | Diabetes, Lipid Disorders, and Obesity (DDLO) |
| **Clinical Reviewers:** | Ginger Winston, MD/Eileen Craig, MD |
| **Associate Director for Labeling:** | CAPT Melinda M Wilson, PharmD, MPH, BCPS, RAC |
| **Division Director:** | John Sharretts, MD |
| **Review Date:** | July 23, 2025 |
| **Goal Date:** | June 18, 2025 |
| **Project Manager:** | Ron Picking |

## PRIOR APPROVAL SUPPLEMENT 45

The Applicant, Amgen Inc., submitted a Prior Approval Supplement (PAS) to update the Repatha SureClick Autoinjector Instructions for Use (IFU), Reference Guide (RG), and secondary packaging including carton label artwork as part of an effort to improve the organization and clarity of the SureClick Autoinjector (AI) instructions. There is no change to the design, operating steps, or user groups of the Repatha SureClick Autoinjector device. Amgen intends to continue to harmonize the IFU across multiple Amgen products that use the SureClick Autoinjector device platform, including Enbrel®, Aimovig®, and Repatha®.

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) was consulted and asked to review the proposed Repatha IFU and carton labeling for areas of vulnerability that may lead to medication errors. They concluded that the IFU and carton labeling could be improved and made recommendations that were conveyed to the Applicant (see review by Damon Birkemeier, PharmD, FISMP in DARRTS dated 5/20/2025, Reference ID: 5594497).

DMEPA 2 was consulted and asked to review the human factors validation study (HFVS) report submitted under BLA 125522/S-045. They concluded that the labeling (IFU and RG) could be improved and made recommendations that were conveyed to the Applicant (see review by Chukwuemeka Okoronkwo, PharmD in DARRTS dated 5/21/2025, Reference ID: 5595262).

Additional labeling reviews include:

- Office of Prescription Drug Promotion Memorandum by Tierra Butler and Sapna Shah dated June 24, 2025. Reference ID: 5613380.
- Patient Labeling Review by Lonice Carter, Tierra Butler, Sharon Williams, and Marcia Williams dated June 25, 2025. Reference ID: 5614306.

The clinical team asked the Applicant to consider changes to the indication statement in the prescribing information (PI) and related changes to the patient package insert (PPI) to simplify the language and improve the clarity of the indication statement for patients and health care providers (details below).

The Applicant submitted revised draft labeling (PI, PPI, IFUs, reference guide, and carton labeling with responses) on June 18, 2025. The DMEPA 2 Human Factors team had no objections to the revisions. The clinical team proposed some minor edits in the PI and PPI to be consistent with the indication revisions.

Label changes for Repatha that were included in this supplement are summarized below:

- PI Section 1: We proposed the following revision of “adults with established cardiovascular disease” to “adults at increased risk for these events” to better describe the population likely to achieve a reduction in MACE events, namely patients who have had a CV event and those at increased risk for a CV event (primary and secondary CV prevention). The details of the trial population are described in Section 14 of the PI.
    - From: To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults with established cardiovascular disease.
    - To: To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults at increased risk for these events.
- PI Section 1: Noting the robust LDL-C lowering and cardiovascular outcome data for the proprotein convertase subtilisin/kexin type 9 inhibitor class, the indication has been simplified to state that Repatha can be used as an adjunct to diet and exercise to reduce low density lipoprotein cholesterol (LDL-C) in populations with hypercholesterolemia, HeFH, and HoFH, based on trial data in these populations.
    - The term ‘exercise’ has been added, similar to the indication for drugs that treat diabetes mellitus, as both diet and exercise are part of the background lifestyle measures recommended to treat hypercholesterolemia. This

change is supported by CFR 201.57( c)(2)(i)(A) that states "[t]his section must include…a statement that the drug is indicated as an adjunct to that mode of therapy".

- The term 'hyperlipidemia' has been changed to 'hypercholesterolemia' because hyperlipidemia is a broader term that refers to cholesterol and triglycerides (TG). Older statin indications included changes in total cholesterol, HDL-C, TG, etc., which have been removed to more accurately focus on LDL-C reduction only. Hypercholesterolemia is more specific than hyperlipidemia, and refers to high levels of cholesterol, particularly LDL-C and apolipoprotein B. We believe this term more accurately describes the specific disease or condition for which the drug is approved (i.e., does not imply that the drug is approved for treatment of elevated triglycerides or other lipids such as Lp(a)), and is more consistent with the indication and labeling for LDL-C lowering therapies more generally.
- Changed from:
  • As an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C
  • As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C
  • As an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C
- To: As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in:
  - adults with hypercholesterolemia.
  - adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
  - adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).

- PI Sections 2.1 Recommended Dosage: Minor edits were made to this section to reflect the indication language.
- PI Sections 6.1, 8.4, and 14: Minor edits were made to reflect the revised indication language, including changing 'hyperlipidemia' to 'hypercholesterolemia'. The term 'primary' has been retained for the heading in Section 14 (Primary Hypercholesterolemia) as the clinical trial population reflects subjects with primary, as opposed to secondary, hypercholesterolemia.

- Revisions were made to the Highlights section of the PI and patient prescribing information (PPI) for consistency with the full prescribing information (PI).

- Additional revisions were made to the applicant's proposed RG, including:

  - In Step 4, clarified cap removal instructions and added cap color to the instructions. Added the black lot/expiry placeholder label to the illustration in Steps 4 and 7.
  - In Step 5 added clarity on the duration that the stretching or pinching should occur to ensure that this continues for the duration of the injection.

- Additional revisions were made to the applicant's proposed IFUs, including:
  - Revised autoinjector illustrations in the IFU in Steps 10, 13, and 14 to show the black lot/expiry placeholder label. The rationale was that the illustration of the user interface should align throughout the IFU to prevent any misinterpretation of device orientation and reduce risk of wrong technique medication error leading to harm.
  - In Step 11 added clarity on the duration that the stretching or pinching should occur to ensure that this continues for the duration of the injection.
  - In Step 15, changed the title language to provide further clarification on the header from 'Disposing of REPATHA and Checking the Injection Site" and updating it to "Completing the Injection and Disposal."

With submission of labeling for supplement-045 on July 22, 2025, the Applicant accepts all of FDA's most recent recommendations for labeling (IFUs, PPI, and PI) and the supplement can be approved.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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EILEEN M CRAIG
07/23/2025 02:30:50 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125522Orig1s045

# OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | August 14, 2025 |
| Requesting Office or Division: | Division of Diabetes, Lipid Disorders, and Obesity (DDLO) |
| Application Type and Number: | BLA 125522/S-045 |
| Product Name, Dosage Form, and Strength: | Repatha (evolocumab) injection, Prefilled syringe: 140 mg/mL; Autoinjector: 140 mg/mL; On-body infusor with prefilled cartridge: 420 mg/3.5 mL |
| Applicant Name: | Amgen Inc |
| FDA Received Date: | August 14, 2025 |
| TTT ID #: | 2025-12479-1 |
| DMEPA 1 Team Leader: | Damon Birkemeier, PharmD, FISMP |
| DMEPA 1 Associate Director for Nomenclature and Labeling: | Idalia E. Rychlik, PharmD |

## 1 PURPOSE OF MEMORANDUM

Amgen Inc submitted revised carton labeling August 14, 2025 for Repatha. Amgen previously submitted revised carton labeling via email received on June 18, 2025. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised carton labeling for Repatha (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 DISCUSSION

Regarding the carton labeling contained in Amgen's email response dated June 18, 2025, Amgen accepted most of our recommendations. However, regarding our recommendation to consider deleting the following statements and accompanying graphics to reduce duplication of information and clutter on the principal display panel (PDP) since the information is already presented on the back panel:

- "Caution, See package insert for full prescribing information and Instructions for Use"
- "Do Not Re-use"
- "Refrigerate until ready to use"

Amgen Inc proposed to retain this information on both the PDP and the back panel, stating "*This duplication is intentional, as it ensures that critical information remains accessible in the event that a pharmacy label is placed such that it covers one of the panels.*" We acknowledge Amgen Inc's rationale and find their proposal reasonable at this time. Additionally, note that our previous recommendation regarding removing the statement "this product contains dry natural rubber" from the PDP was not conveyed to Amgen Inc after discussion with DDLO.

Regarding the expiration date, Amgen Inc clarified "*the current format of their expiration date on the container and carton labels is DDMMMYYYY, using three alphabetical characters for the month, two-digit numerals for the day, and four-digit numerals for the year (e.g. 31OCT2024).*"

Regarding the machine readable (2D data matrix barcode) product identifier, Amgen Inc confirmed *"a place holder on the carton labeling for the machine-readable (2D data matrix) barcode is on the current configuration as shown in Figure 1. The machine-readable (2D data matrix) barcode for the carton will be printed near the human-readable portion of the product identifier on the packaging line at the time of production."* See Figure 1.

[a] Birkemeier D. Label and Labeling Review for Repatha (BLA 125522/S-045). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAY 20. TTT ID: 2025-12479.

Figure 1. 2D Data Matrix Code


Amgen Inc proposed to *"update the dose dot color to blue to align with Repatha's 140 mg label on all carton panels. This aligns with the dose color of in-market labelling. In addition, Amgen has removed the blue background from the Primary Display Panel (PDP) and the bottom panel to enhance contrast and readability."* We find the proposal to update the dose dot color acceptable from a medication error perspective.

Regarding our recommendation for the 140 mg/mL autoinjector two-pack to retain the previously approved image of two AIs on the principal display panel (PDP) to increase differentiation from the 140 mg/mL AI one-pack carton labeling, Amgen proposed to keep the single autoinjector image on the PDP of the carton, stating *"Repatha 1 count (replacement packs) and Repatha 2 count are distinguished by different National Drug Codes (NDC) that will ensure accurate dispensing of these products in pharmacies. However, Amgen suggests harmonizing with other SureClick cartons by relocating the manufacturing information from the front panel to the bottom panel and adding of the quantity of autoinjectors (2) on the side panels. This will further distinguish between the single and two-count cartons. This ensures consistency with other SureClick products and is aligned with recent agency feedback on Enbrel carton labeling."* While we acknowledge Amgen's response, we believe the previously approved image of two AIs on the PDP provides increased differentiation. Understanding that the currently marketed two-pack contains an image of two devices, we are concerned that revision of the image to remove both devices may lead to inadvertent dispensing errors. Thus, we continue to recommend retaining the image of two AIs on the principal display panel (PDP) for the two-pack.

Thus, we conveyed the following recommendation to Amgen Inc via email:

- While we acknowledge your previous response regarding our recommendation for the 140 mg/mL autoinjector two-pack to retain the previously approved image of two AIs on the principal display panel (PDP) to increase differentiation from the 140 mg/mL AI one-pack carton labeling, we believe the previously approved image of two AIs on the PDP provides increased differentiation. Understanding that the currently marketed two-pack contains an image of two devices, we are concerned that revision of the image to remove both devices may lead to inadvertent dispensing errors. Thus, we continue to recommend retaining the image of two AIs on the principal display panel (PDP) for the two-pack. Alternatively, given the text burden on the PDP, to increase differentiation between the 140 mg/mL autoinjector two-pack from the 140 mg/mL AI one-pack carton labeling, you may consider increasing the prominence of the entirety of the net quantity

statement on the PDP by taking into account all pertinent factors including font size, type, and color; background contrast; and statement location.

On July 22, 2025, Amgen Inc replied via email to our recommendation above, proposing to increase the size of the text (b) (4) See Figure 2. below for an example of the updated 2 pack carton labeling that was included with Amgen's email response.

**Figure 2. Repatha (evolocumab) 140 mg/mL SureClick Autoinjector 2-pack Carton Labeling received via email on July 22, 2025**

(b) (4)

We reviewed Amgen Inc's proposal and determined that the proposal to increase the size of the net quantity statement on the PDP was acceptable; however, we found the proposal to (b) (4)

(b) (4)

On July 25, 2025, Amgen replied via email to our recommendations above and agreed to remove (b) (4)
(b) (4)

## 3 CONCLUSION

The revised carton labeling is acceptable from a medication error perspective, and we have no additional recommendations at this time.

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JASON A FLINT on behalf of IDALIA E RYCHLIK
08/15/2025 07:59:13 AM

**Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**

**and**

**Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)**

**Labeling Review**

| | |
|---|---|
| **Application Type and Number** | BLA 125522/S-045 |
| **Date of Receipt** | December 19, 2024 |
| **Applicant** | Amgen, Inc. |
| **Proprietary Name (nonproprietary name) dosage form** | Repatha (evolocumab) injection |
| **DDLO Reviewers** | Melinda Wilson, PharmD, MPH, BCPS, RAC<br>Associate Director for Labeling, DDLO |
| **DRO-CHEN Regulatory Project Manager (RPM)** | Ron Picking, PharmD |
| **DRO-CHEN RPM Supervisory Concurrence** | Elizabeth Solomon, MSHS, CCRP, RAC-Drugs, GWCPM |

**Labeling Reviewed**

**Background and Regulatory History of Application**

Repatha is a proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9) currently indicated:

- To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults with established cardiovascular disease
- as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C
- as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C
- as an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C

On December 19, 2024, Supplement 45 was submitted proposing to update the SureClick Autoinjector (AI) Reference Guide (RG), carton and container labeling, and latex-containing and latex-free AI Instructions for Use (IFU) to improve clarity of instructions and harmonize the labeling across multiple Amgen products.

During the review cycle, the FDA made changes to the Prescribing Information (PI) to revise the indication to:

Repatha is indicated:

- To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults at increased risk for these events.
- As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in:
    - adults with hypercholesterolemia.
    - adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
    - adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).

The Patient Package Insert (PPI) was revised to reflect the changes to the PI.

**Review**

The final agreed labeling received on July 22, 2025, was compared to the currently approved PI, PPI, and IFUs approved with Supplement 44 on November 20, 2024, and the RG approved with Supplement 33 on August 16, 2022. See attached labeling for description and commentary on specific revisions.

For a full list of recommendations, please see the following reviews in DARRTS:

- Label and Labeling Review by Damon Birkemeier and Idalia Rychlik dated May 20, 2025. Reference ID: 5594497.
- Human Factors Study Report Review by Chukwuemeka Okoronkwo, Colleen Little, Lolita Sterrett, and Hina Mehta dated May 21, 2025. Reference ID: 5595262.
- Office of Prescription Drug Promotion Memorandum by Tierra Butler and Sapna Shah dated June 24, 2025. Reference ID: 5613380.
- Patient Labeling Review by Lonice Carter, Tierra Butler, Sharon Williams, and Marcia Williams dated June 25, 2025. Reference ID: 5614306.
- Prior Approval Labeling Supplement – Clinical Memo by Eileen Craig dated July 23, 2025. Reference ID: 5630082.
- Review of Revised Label and Labeling by Damon Birkemeier and Idalia Rychlik dated August 15, 2025. Reference ID: 5643439.

**Regulatory Recommendations**

The labeling was reviewed and found acceptable. This supplement is ready for approval. The Agency should issue an approval letter for this supplement.

**Attachments:**

Final draft labeling, with revisions annotated.

*See appended electronic signature page.*

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**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 25, 2025 |
| To: | Ron Picking, Pharm.D.<br>Regulatory Project Manager<br>**Division of Diabetes, Lipid Disorders, and Obesity (DDLO)** |
| Through: | Marcia Williams, PhD<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Sharon Williams, MSN, BSN, RN<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Lonice Carter, MS, RN, CNL, NHDP-BC<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Tierra Butler, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Instructions for Use (IFUs) and Reference Guide |
| Drug Name (established name): | Repatha (evolocumab) |
| Dosage Form and Route: | injection, for subcutaneous use |
| Application Type/Number: | BLA 125522 |
| Supplement Number: | S-045 |
| Applicant: | Amgen, Inc. |

# 1 INTRODUCTION

On December 19, 2024, Amgen, Inc. submitted for the Agency's review a Prior Approval Supplement – Labeling for supplemental Biologics License Application 125522/ S-045 Repatha (evolocumab) injection, for subcutaneous use. This supplemental application proposes changes to the Repatha SureClick Autoinjector Instructions for Use (IFU), Reference Guide (RG), and carton labeling to improve organization and clarity of the SureClick Autoinjector instructions.

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 Diabetes, Lipid Disorders, and Obesity (DDLO) on January 8, 2025, for DMPP and OPDP to review the Applicant's proposed IFU and RG for Repatha (evolocumab) injection, for subcutaneous use.

# 2 MATERIAL REVIEWED

- Draft Repatha (evolocumab) IFU and RG received on December 19, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 16, 2025.
- Draft Repatha (evolocumab) Prescribing Information (PI) received on December 19, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 17, 2025.

# 3 REVIEW METHODS

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

In our collaborative review of the IFU and QRG we:

- simplified wording and clarified concepts where possible
- ensured that the IFU and QRG are consistent with the PI
- removed unnecessary or redundant information
- ensured that the IFU and QRG are 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 both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

## 4 CONCLUSIONS

The IFU and QRG are 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 and QRG 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 and QRG.

Please let us know if you have any questions.

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**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** June 24, 2025

**To:** Ronald Picking III, Regulatory Project Manager, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN) for the Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Ginger Winston, Clinical Reviewer, DDLO
Eileen Craig, Clinical Reviewer, DDLO

Melinda Wilson, Associate Director for Labeling, DDLO

**From:** Tierra Butler, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Sapna Shah, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for REPATHA (evolocumab) injection, for subcutaneous use

**BLA**: 125522, S-045

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**Background:**
In response to DDLO's consult request dated January 8, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for supplement 45 for Repatha (evolocumab) injection, for subcutaneous use. This supplement updates the Repatha SureClick autoinjector IFUs (latex-containing and latex-free), reference guide, and carton labeling to improve clarity of instructions.

**PI/PPI/IFU/Reference Guide :**
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 17, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU, and comments will be sent under separate cover.

**Carton and Container Labeling**:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on June 24, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Tierra Butler at (301) 796-1368 or tierra.butler@fda.hhs.gov.

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TIERRA N BUTLER
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HUMAN FACTORS STUDY REPORT REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | May 21, 2025 |
| Requesting Office or Division: | Division of Diabetes, Lipid Disorders, and Obesity (DDLO) |
| Application Type and Number: | BLA 125522/S-045 |
| Product Type: | Combination Product (Biologic-Device) |
| Product Name, Dosage Form and Strength: | Repatha (evolocumab) injection, 140 mg/mL |
| Device Constituent: | Autoinjector |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Amgen, Inc. |
| FDA Received Date: | December 19, 2024, March 20, 2025, April 14, 2025 |
| TTT ID #: | 2025-12497 |
| DMEPA 2 Safety Evaluator: | Chukwuemeka Okoronkwo, PharmD |
| DMEPA 2 Team Leader: | Colleen Little, PharmD |
| DMEPA 2 Associate Director for Human Factors: | Lolita Sterrett, PharmD |
| DMEPA 2 Associate Director for Nomenclature and Labeling | Hina Mehta, PharmD |

# 1 REASON FOR REVIEW

On 12/19/2024, Amgen, Inc. submitted the following Prior Approval Supplements (PASs) to update the autoinjector (AI) Instructions for Use (IFU), Reference Guide (RG), and carton labeling "as part of a continuous effort to improve the organization and clarity of the SureClick Autoinjector (AI) instructions" and "to continue to harmonize the IFU across multiple Amgen products that use the SureClick Autoinjector device platform."[a]

- BLA 125522/S-045 for Repatha (evolocumab) 140 mg/mL
- BLA 761077/S-025 for Aimovig (erenumab-aooe) 70 mg/mL and 140 mg/mL
- BLA 103795/S-5603 for Enbrel (etanercept) 50 mg/mL

This review evaluates the human factors validation study (HFVS) report submitted under BLA 125522/S-045. The HFVS report submitted under BLA 103795/S-5603 and BLA 761077/S-025 are evaluated under separate covers[b,c].

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

| Material Considered | Section/Appendix |
|---|---|
| Product Information | Section 1.1 |
| Relevant Regulatory History Related to the Proposed Product's Human Factors Development Program | Section 1.2 |
| Human Factors (HF) Validation Study Report and HF-Related Supporting Documents | Appendix A |
| Information Requests Issued During the Review | Appendix B |
| Labeling | Appendix C |
| Tasks Involving Use Errors, Use Difficulties, and Close Calls for Section 3.1 | Appendix D |

N/A=not applicable for this review

## 1.1 PRODUCT INFORMATION

[a] Cover Letter- PAS Repatha SureClick Next Generation IFU (Aimovig BLA 125522/S-045). Thousand Oaks (CA): Amgen Inc; 2024 DEC 19. Available from: \\CDSESUB1\EVSPROD\bla125522\0395\m1\us\12-cover-letters\cover-letter.pdf.

[b] Okoronkwo, C. Human Factors Results Review for Enbrel (BLA 103795/S-5603). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAY 21. TTT ID No.: 2025-12516.

[c] Okoronkwo, C. Human Factors Results and Labeling Review for Aimovig (BLA 761077/S-025). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAY 21. TTT ID No.: 2025-12986, 2025-12977.

Table 2 presents relevant product information for the AI presentation of Repatha that Amgen, Inc. submitted on December 19, 2024 and from the currently approved Prescribing Information (PI).[d]

| **Table 2. Relevant Product Information for Repatha** | |
|---|---|
| **Initial Approval Date** | 8/27/2015 |
| **Active Ingredient** | evolocumab |
| **Indication** | • to reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults with established cardiovascular disease<br>• as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C<br>• as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C<br>• as an adjunct to other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C |
| **Route of Administration** | Subcutaneous (SQ) |
| **Dosage Form** | Injection |
| **Strength** | 140 mg/mL |
| **Dose and Frequency** | In adults with established cardiovascular disease or with primary hyperlipidemia:<br>• the recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously.<br>• if switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.<br>In pediatric patients aged 10 years and older with HeFH: |

[d] Repatha [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. NOV 2021. [cited 2025 APR 01]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125522s044lbl.pdf.

| | |
|---|---|
| | • the recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously.<br>• if switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.<br>In adults and pediatric patients aged 10 years and older with HoFH:<br>• the initial recommended dosage of REPATHA is 420 mg once monthly administered subcutaneously.<br>• the dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. |
| How Supplied | 140 mg/mL solution single-dose prefilled SureClick autoinjector |
| Storage | Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.<br><br>For convenience, REPATHA may be kept at room temperature at 68°F to 77°F (20°C to 25°C) in the original carton for 30 days. If not used within the 30 days, discard REPATHA. |
| Container Closure/ Device Constituent (including figure) | <u>SureClick Autoinjector</u><br>  |
| Intended Users | Healthcare Professionals (HCPs), patients aged 18 years of age and older, pediatric patients aged 10 to 17 years old, caregivers |
| Intended Use Environment | Clinical, Home |

## 1.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On March 17, 2025, we searched for previous DMEPA reviews and FDA/Amgen, Inc. interactions relevant to this current review using the terms, "Repatha," "evolocumab," and "125522." The identified reviews and FDA/Amgen, Inc. interactions are provided below.

- On February 16, 2022, Amgen, Inc. submitted labeling supplements for Repatha (BLA 125522/S-03), Enbrel (BLA 103795/S-5591), and Aimovig (BLA 761077/S-016) to harmonize the IFUs and RGs across the SureClick autoinjector platform. We determined

the Repatha IFU and RG were acceptable from a medication error perspective and we did not provide recommendations regarding the Repatha labeling.[e]

- On December 21, 2023, Amgen, Inc. submitted a PAS under BLA 125522/S-043 to continue to harmonize the IFUs across multiple Amgen drugs that use the SureClick AI device platform as part of a continuous effort to improve the SureClick AI instructions in terms of readability and comprehension.[f] This PAS included a use-related risk analysis (URRA) and comparative analyses between the revised Repatha IFU and the approved Amjevita (BLA 761024/S-015) IFU to support the revisions to the proposed Repatha IFU and to justify their determination that no further human factors (HF) data was needed. Amgen, Inc. submitted similar PASs under:
    - Aimovig (BLA 761077/S-022) received on February 7, 2024 and
    - Enbrel (BLA 103795/S-5597) received on January 23, 2024.

  On May 1, 2024, we found the proposed Repatha IFU acceptable from a medication error perspective and did not provide any recommendations to Amgen, Inc.[g]
- On December 19, 2024, Amgen, Inc. submitted a PAS along with the results from a HFVS study and labeling under BLA 125522/ S-045 for Repatha, BLA 103795/S-5603 for Enbrel, and BLA 761077/S-025 for Aimovig. Our evaluation of the HFVS results relevant to Repatha is the subject of this review.

## 2 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design, and our evaluation of the study methodology to determine if the study has been appropriately designed to support the safe and effective use of the proposed product.

### 2.1 SUMMARY OF STUDY DESIGN

Amgen, Inc. conducted a single HFVS to evaluate the proposed changes to the IFUs, RGs, and carton labeling for Aimovig, Enbrel, and Repatha. Table 3 presents a summary of the HF validation study (HFVS) design and our discussion of methodology concerns (as applicable). Amgen, Inc. did not submit the HFVS protocol for FDA's review prior to commencing the HFVS. See Appendices A and B for more details on the study design.

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[e] Vee, S. Label and Labeling Review for Repatha, Aimovig, and Enbrel (BLA 125522/S-033; BLA 761077/S-016; BLA 103795/S-5591) Silver Spring (MD): FDA, CDER, DMEPA (US); 2020 NOV 19. RCM No.: 2022-475; 2022-480; 2022-504.

[f] Cover Letter for Repatha (BLA 125522/S-043). Thousand Oaks, CA: Amgen Inc.; 2023 DEC 21. Available from: \\CDSESUB1\EVSPROD\bla125522\0373\m1\us\12-cover-letters\cover-letter.pdf.

[g] Barlow, M. Use-Related Risk Analysis and Comparative Analyses Review for Enbrel (BLA 103795/S-5597) and Repatha (BLA 125522/S-043). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 01. TTT ID No.: 2024-7801; 2024-8038.

Table 3. Study Methodology for Human Factors (HF) Validation Study[h]

| Study Design Elements | DMEPA Discussion of Methodology Concerns |
|---|---|

| User Group | Injection experience | Injection naïve |
|---|---|---|
| Caregivers (n=23) | 12 | 11 |
| HCPs (n=15) | 15 | N/A |
| Aimovig arm | | |
| Adult patients (n=15) | n=8 | n=7 |
| Pediatric patients (n= 15) | n=7 | n=8 |
| Enbrel arm | | |
| Adult patients (n= 15) | n=8 | n=7 |
| Pediatric patients (n= 15) | n=8 | n=7 |
| Repatha arm | | |
| Adult patients (n= 15) | n=8 | n=7 |
| Pediatric patients (n= 15) | n=8 | n=7 |

Per Amgen, Inc., the caregiver and HCP user groups were considered drug agnostic (e.g. do not share indication specific limitations). Therefore, the participants in these user groups split between each arm of the study as follows:

- Aimovig arm
  - 8 caregivers interacted with the Aimovig user interface (IU)
  - 5 HCPs interacted with the Aimovig UI
- Enbrel arm
  - 8 caregivers interacted with the Repatha IU
  - 5 HCPs interacted with the Repatha IU
- Repatha arm

Caregiver and HCP User Groups:

While the UIs for Aimovig, Enbrel, and Repatha are similar, they are not identical regarding tasks and UI design. For example, per the Instructions for Use for each product, only Enbrel users are instructed to select a different site for each injection.

We generally expect a minimum of 15 HCP and 15 Caregiver participants per distinct user group. However, based on the extent and type of the proposed changes, considering no device changes are proposed in this supplement, our evaluation of these changes, and our employment of labeling best practices to ensure the proposed changes support safe and effective use; we find that the approach of a combined 15 member HCP and combined 15 member Caregiver group for all three arms does not preclude our review in this particular instance.

Adult Patient User Groups:

We note Amgen recruited patient participants for this study who may not have previously interacted with the product being evaluated. Based on the scope of this study (e.g. changes to the existing labeling) a more robust user group would have been the patient user who had

[h] This table provides the study methodology for the entire HFVS which included 3 arms (i.e., Aimovig arm, Enbrel arm, and Repatha arm) ; however, the reported performance data for each arm is evaluated under separate covers (see Section 1 above).

| Table 3. Study Methodology for Human Factors (HF) Validation Study[h] | |
|---|---|
| Study Design Elements | DMEPA Discussion of Methodology Concerns |
| ▪ 7 caregivers interacted with the Repatha IU<br>▪ 5 HCPs interacted with the Repatha IU<br><br>Per Amgen, Inc., the injection experienced patient participant user group included only surrogates in the Repatha arm of the study to represent the intended patient population. (e.g., Repatha patient participants were recruited based on specific characteristics such as hypercholesterolemia and may not have previously interacted with the currently marketed Repatha UI). | experience with the previous labeling. Because Amgen did not submit their HF validation study protocol for our review prior to conducting the study and submitting results, we did not provide comments or guidance on the preferred characteristics of the adult patient user groups. However, this approach does not preclude our review in this particular instance. |
| Training | |
| No training provided | |
| Test Environment & Materials | |
| Test Environment<br>• The HFVS was performed in representative use environments.<br>• The study room was configured to include tables, chairs, and a trash can.<br>Study Materials<br>• AI[i] , IFU, RG, PI, and secondary packaging/carton labeling<br>• Sharps container, alcohol wipes, bandages, and hand sanitizer<br>• Video equipment visibly used to record sessions | |
| Sequence of Study | |
| • Rapid COVID-19 Testing<br>• Consent & Confidentiality Agreement<br>• Demographics Questions. Rapid Estimate of Adult Literacy in Medicine – Short Form (REALM-SF) and Study Introduction | Amgen, Inc. states "per the study, root cause probing was limited to critical tasks". Therefore, Amgen did not submit subjective feedback or RCA data regarding use errors, close calls, or use difficulties that occurred |

[i] Aimovig and Repatha AIs included placebo. Enbrel AIs included actual drug product.

| Table 3. Study Methodology for Human Factors (HF) Validation Study[h] | |
|---|---|
| Study Design Elements | DMEPA Discussion of Methodology Concerns |
| • Scenario 1 – Evaluation of Storage Tasks (Knowledge Assessment Questions)<br>• Scenario 2 – Simulated Use<br>• Root Cause Analysis (RCA)<br>• Knowledge Assessment Questions<br>• RCA<br>• Tray Interior Feedback (time permitting)<br>• Conclusion, Dismiss, and Compensate | during the HFVS for any non-critical task.<br><br>We generally expect HFVS reports to include the Applicant's evaluation of use errors, close calls, and use difficulties, along with the RCA for all tasks. However, based on the extent and type of the proposed changes to the non-critical tasks, our evaluation of these changes, and our use of labeling best practices to ensure the proposed changes support safe and effective use; we find that the lack of subjective feedback and RCA data for non-critical tasks does not preclude our review in this particular instance. |

## 3 RESULTS AND ANALYSIS

In this section, we have carefully reviewed each reported issue (i.e., use errors and use difficulties or close calls), the Applicant's URRA, the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments and proposed mitigations (if applicable) to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. In Table 4 below, we provide a summary of the use-related events supplied by the Applicant along with our detailed analysis of use-related events that resulted in recommendations and document our points of dissent with the Applicant's findings.

<table>
<tr><th colspan="3">Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations for the Repatha study arm</th></tr>
<tr><td colspan="3">Legend: UE = use error; CC = close call; UD = use difficulty; URRA = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study; HF =Human Factors; HCP = Healthcare professional; RG = Reference Guide; IFU = Instructions for Use; AI = Autoinjector; SC= SureClick</td></tr>
<tr><th></th><th>Summary of Information Supplied by Applicant</th><th>DMEPA's Identified Areas of Dissent and Recommendations</th></tr>
<tr><td>1.</td><td>Task: User properly removes cap from SC device just before injection<br>Scenario 2: Simulated Use<br><br><table><tr><th>Reported Issues:</th><th>Participant Type(s):</th></tr><tr><td>UE (n=5)</td><td>1 HCP<br>1 Adult Patient<br>2 Adolescent Patients<br>1 Caregiver</td></tr><tr><td>CC or UD (n=4)</td><td>1 Adult Patient<br>1 Adolescent Patient<br>2 Caregivers</td></tr></table></td><td></td></tr>
<tr><td></td><td>Observed event(s):<br>• User expressed difficulty identifying and/or removing the cap as intended (e.g. twisted instead of pulled)</td><td></td></tr>
<tr><td></td><td>Potential harm associated with issues for this task:<br>• Decreased efficacy, underdose</td><td></td></tr>
<tr><td></td><td>Relevant RCA/Subjective Feedback:<br>• The information to not twist the needle cap during removal was not included in the RG</td><td></td></tr>
<tr><td></td><td>Applicant's Comments and Proposed Post- HFVS Mitigations:<br>• The Applicant determined that no additional change to the user interface is needed to address the residual risk for this use task.</td><td>Based on our review of the subjective feedback and root cause analysis for these use errors and use difficulties or close calls, we disagree with the Applicant and have determined additional labeling mitigations could be implemented to ensure safe and intended use in the removal of the cap. We provide our recommendation below in Table 5. This recommendation can be implemented without the submission of additional HF data.</td></tr>
<tr><td>2.</td><td>Task: User stretches or pinches skin<br>Scenario 2: Simulated Use<br><br><table><tr><th>Reported Issues:</th><th>Participant Type(s):</th></tr><tr><td>UE (n=6)</td><td>1 HCP<br>7 Adult Patients<br>1 Adolescent Patient</td></tr></table></td><td></td></tr>
<tr><td></td><td>Observed event(s):</td><td></td></tr>
</table>

| Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations for the Repatha study arm | | |
|---|---|---|
| **Legend**: **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis; **HFVS** = Human Factors Validation Study; **HF** =Human Factors; **HCP** = Healthcare professional; **RG** = Reference Guide; **IFU** = Instructions for Use; **AI** = Autoinjector; **SC**= SureClick | | |
| | Summary of Information Supplied by Applicant | DMEPA's Identified Areas of Dissent and Recommendations |
| | • User either did not pinch or stretch the skin at the injection site as instructed or did not keep pinching/stretching for the duration of the injection. | |
| | Potential harm associated with issues for this task:<br>• Decreased efficacy, underdose | |
| | Relevant RCA/Subjective Feedback:<br>• Participant explained they read and understood to pinch the skin but did not pinch for the duration of the injection because they did not see the information in the RG. | |
| | Applicant's Comments and Proposed Post- HFVS Mitigations:<br>• Applicant updated RG language to state "Stretch or pinch the skin to create a firm surface at the injection site."<br>• Illustration revised with the addition of the AI. Also, the skin color has been muted.<br>• Call-out texts revised to: "STRETCH" and "PINCH."<br>• Revised style of "OR" to black background with white font. | Based on our review of the subjective feedback and root cause analysis for these use errors, we have determined additional mitigations should be implemented to prevent wrong technique medication error resulting in decreased efficacy/underdose. We provide our recommendation below in Table 5. This recommendation can be implemented without the submission of additional HF data. |

## 3.1 ANALYSIS OF THE REMAINING IDENTIFIED ISSUES

The HF validation study report showed issues with the tasks evaluated by simulated use and knowledge task assessments listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), the Applicant's root cause analysis, and our evaluation of the residual risks, and post-HFVS changes to the user interface; we have no additional recommendations to address the identified issues with the tasks in Appendix D.

## 3.2 COMMUNICATION OF OUR ANALYSIS TO THE DMEPA 1 HF REVIEW TEAM

Because this review includes indications outside of the Division of Medication Error Prevention and Analysis (DMEPA) 2 HF team purview, we communicated our findings to the DMEPA 1 HF team via e-mail on May 20, 2025. The DMEPA 1 HF team did not provide any additional feedback regarding DMEPA 2's findings or recommendations.

## 4 LABELS AND LABELING

Table 5 below includes the identified medication error issues with the submitted product samples, packaging, and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated product specific labeling under a separate cover.[j]

**Table 5. Identified Issues and Recommendations for Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**

| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
|---|---|---|---|
| **Reference Guide** | | | |
| 1. | Based on the submitted HF validation study (HFVS) results, we note participants had difficulty understanding how to remove the cap correctly.<br><br>Specifically, participants attempted to remove the cap incorrectly by twisting versus pulling the cap straight off. | This failure to pull the cap straight off has the associated potential harm of an underdose or no dose medication error.<br><br>In addition, because your mitigation discussion from the simulated use study states that the cap color is designed to aid identification of the needle end, we find it reasonable to also describe the cap color in step 4 of your Reference Guide (RG). We note this cap color description already exists in the Instructions for Use (IFU). | To improve clarity and understanding on the proper way to remove the cap, we recommend replacing the proposed language (b) (4) [redacted] with the following language similar to the current statement in step 2 of the marketed RG in bold font to now read: "Pull the orange cap straight off only when you are ready to inject within 5 minutes – the medicine can dry out."<br><br>Additionally, update your use-related risk analysis to evaluate the potential use issue of twisting the cap along with any potential harm associated with this use issue. |

[j] Birkemeier, D. Label and Labeling Review for Repatha (evolocumab) injection (BLA 125522/S-045). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAY 20. TTT ID No.: 2025-12479.

| Table 5. Identified Issues and Recommendations for Division of Diabetes, Lipid Disorders, and Obesity (DDLO) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| 2. | As currently presented, the autoinjector illustrations in the RG step 4, step 7, step 8 may lead to wrong technique medication error because they do not include the black lot/expiry placeholder label.<br><br>In addition, we note as part of your documented known use assessment of your device, you state incorrect orientation of the autoinjector (e.g., upside down) resulting in accidental thumb injection. | The illustration of the user interface should align throughout the RG to prevent any misinterpretation of proper device orientation and reduce risk of wrong technique medication error leading to harm. | Revise the autoinjector illustrations to show the black lot/expiry placeholder label in steps 4, 7, and 8. |
| Instructions for Use | | | |
| 1. | As currently presented, the autoinjector illustration in the IFU above steps 10, 13, and 14 may lead to wrong technique medication error because they do not include the black lot/expiry placeholder label and is not in alignment with the "Getting to know your prefilled autoinjector" section. | The illustration of the user interface should align throughout the IFU to prevent any misinterpretation of device orientation and reduce risk of wrong technique medication error leading to harm. | Revise autoinjector illustrations in the IFU above steps 10, 13, and 14 to show the black lot/expiry placeholder label. |
| 2. | As proposed, the location of important dose confirming | We are concerned that underdose medication errors may occur if users | Relocate the title (b) (4) o appear immediately |

| | | | |
|---|---|---|---|
| | information can be improved to decrease risk of medication error. Specifically, the title of step 15 (b) (4) is incorrectly presented under the section title (b) (4) " | read (b) (4) before referring to the text and corresponding illustration in step 15. | above the text and corresponding graphic for step (b) (4) |
| **Instructions for Use and Reference Guide** | | | |
| 3. | As currently presented and based on subjective feedback from the HFVS, the IFU and RG can be improved by increasing the prominence of the instructions to stretch or pinch the injection site and adding clarity on the duration that the stretching and pinching should occur. | We are concerned that lack of clarity regarding stretching or pinching the skin for the duration of the injection may lead to confusion resulting in underdose errors. | Revise the RG and IFU to highlight the instructions to stretch and pinch the skin at the site of injection for the duration of the injection as follows:<br>Revise step 5 of the RG from (b) (4) (b) (4) to "Stretch or pinch the skin to create a firm surface at the injection site until the injection is finished."<br><br>In step 11 of the IFU, revise (b) (4) to "Stretch or pinch the skin to create a firm surface at the injection site until the injection is finished."<br>Additionally, remove the bulleted statement (b) (4) " |

## 5 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated issues (i.e., use errors and use difficulties or close calls) with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the issues.

Additionally, our evaluation of the proposed labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 5 for the Division.

APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report and background information can be accessed in EDR via:\\CDSESUB1\EVSPROD\bla125522\0395\m5\53-clin-stud-rep\535-rep-effic-safety-stud\homozygous-familial-hypercholesterolemia\5354-other-stud-rep\rpt-592686\rpt-592686.pdf

- The use-related risk analysis can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla125522\0395\m5\53-clin-stud-rep\535-rep-effic-safety-stud\homozygous-familial-hypercholesterolemia\5354-other-stud-rep\rpt-586803\rpt-586803.xlsx

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On March 17, 2025, we issued an Information Request (IR) to request the following:

- side-by-side comparisons between the currently marketed and proposed IFUs, RGs, and carton labeling for Aimovig (erenumab-aooe) BLA 761077, Enbrel (etanercept) BLA 103795, and Repatha (evolocumab) BLA 125522.
- confirmation regarding any proposed changes to the container labels for the aforementioned products.
- a single summary performance data table that provides performance data for each arm in the HFVS.

On March 20, 2025, the Applicant provided a response that can be accessed in EDR via:

- Side-by-side comparisons: \\CDSESUB1\EVSPROD\bla125522\0405\m5\53-clin-stud-rep\535-rep-effic-safety-stud\homozygous-familial-hypercholesterolemia\5354-other-stud-rep\response-hf-ir\response-hf-ir.pdf
- Summary performance data table: \\CDSESUB1\EVSPROD\bla125522\0405\m5\53-clin-stud-rep\535-rep-effic-safety-stud\homozygous-familial-hypercholesterolemia\5354-other-stud-rep\hf-ue-summary\appx-468401.pdf

On April 10, 2025, we issued an IR to request the moderator script and sequence of study for the submitted HFVS study. On April 14, 2025, the Applicant provided a response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla125522\0406\m5\53-clin-stud-rep\535-rep-effic-safety-stud\homozygous-familial-hypercholesterolemia\5354-other-stud-rep\response-hf-ir\hf-ir-11apr2025.pdf

APPENDIX C. LABELING

C.1 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error experiences with similar products, we reviewed the following Repatha labels and labeling submitted by Amgen, Inc. on December 19, 2024.

- Carton labeling
- Tray Labeling
- Professional Sample Carton Labeling
- Instructions for Use, available from:
    - DNR version: \\CDSESUB1\EVSPROD\bla125522\0395\m1\us\114-labeling\draft\labeling\d-repatha-dry-natural-rubber-ai-ifu-vxx-c-2024-1219.pdf
    - DNR-Free version: \\CDSESUB1\EVSPROD\bla125522\0395\m1\us\114-labeling\draft\labeling\d-repatha-latex-free-ai-ifu-vxx-c-2024-1219.pdf
- Reference Guide, available from: \\CDSESUB1\EVSPROD\bla125522\0395\m1\us\114-labeling\draft\labeling\mck06403-art.pdf

C.2 Labeling and Packaging Images

Carton labeling

1 count, dry natural rubber (DNR)-Free

(b) (4)

2 count, DNR-Free

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX D. TASKS INVOLVING USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FOR SECTION 3.1

Simulated use tasks:

- User removes the IFU
- Wash hands thoroughly with soap and water
- Select injection site for injection
- Clean site with alcohol wipe
- User places the SureClick (SC) safety guard on the pinched or stretched skin
- User fully compresses safety guard of SC device on injection site
- User presses activation button (while maintaining safety guard compression)
- User maintains safety guard compression during injection until injection is complete
- User removes the SC device from the injection site after injection is complete
- Check injection site for any post-injection care
- User disposes SC AI device

Knowledge tasks:

- User properly stores cartons
    - Let's assume that you just got back home from the pharmacy with this autoinjector, and you won't be giving yourself an injection until tomorrow. What should you with the autoinjector until you use it tomorrow? Answer: Refrigerator or the indicated storage range on the carton
    - Let's say I received the product today but won't use it for a while. How and where should I store the product? Answer: Refrigerate until ready to use.
    - My medication froze; can I use it? Answer: No
    - I left my autoinjector at room temperature, how long can it be stored at room temperature? Answer: 30 days
    - Are there any temperatures (conditions) you should avoid storing your autoinjector at? Answer: Extreme heat or extreme cold
- User allows drug to reach room temperature prior to injecting
    - I need to give myself an injection, so I removed an autoinjector from the refrigerator. When can I inject the medication? Answers: Wait 30 minutes or wait to come to room temperature.
- User inspects carton for damage and tampering
    - How would you know if the carton had been tampered with or previously opened? Answer: Tamper evident seal
- User allows drug to reach room temperature prior to injecting
    - I need to give myself an injection, so I removed an autoinjector from the refrigerator. When can I inject the medication? Answers: Wait 30 minutes or wait to come to room temperature.
- User checks device expiration date before administering

    - Does my device have an expiration date and where can I find it? Answer: Check the expiration date on the autoinjector label (box AND/OR device) and do not use if expired.
- User visually inspects SC device(s) for damage
    - How can I tell if the product is safe for use? Answer: Check the device for damage
    - You store multiple medications in the refrigerator. How do you know you're taking the right medication? Answer: Check the AI label or carton for correct medicine and/or dose.
    - I dropped the autoinjector on a hard surface before I was going to use it. Can I still use it? Answer: No.
- User properly removes cap from SC device just before injection
    - I just uncapped the autoinjector. When should I inject after removing the cap? Answer: Any timeframe within 5 min.
- User selects injection site for injection When I'm deciding where to inject, are there any areas or types of skin that I should avoid? Answer: Avoid areas with scars, stretch marks, tender or bruised skin

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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HINA S MEHTA
05/21/2025 04:38:18 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | May 20, 2025 |
| Requesting Office or Division: | Division of Diabetes, Lipid Disorders, and Obesity (DDLO) |
| Application Type and Number: | BLA 125522/S-045 |
| Product Name, Dosage Form, and Strength: | Repatha (evolocumab) injection, Prefilled syringe: 140 mg/mL; Autoinjector: 140 mg/mL; On-body infusor with prefilled cartridge: 420 mg/3.5 mL |
| Product Type: | Combination Product (Biologic-Device) |
| Rx or OTC: | Prescription (Rx) |
| Applicant Name: | Amgen Inc |
| FDA Received Date: | December 19, 2024 |
| TTT ID #: | 2025-12479 |
| DMEPA 1 Team Leader: | Damon Birkemeier, PharmD, FISMP |
| DMEPA 1 Associate Director for Nomenclature and Labeling | Idalia E. Rychlik, PharmD |

## 1 INTRODUCTION

Amgen Inc submitted a Chemistry Manufacturing and Controls (CMC) - Prior Approval Supplement (PAS) for Repatha (evolocumab) injection to update the Repatha SureClick Autoinjector Instructions for Use (IFU), Reference Guide (RG), and secondary packaging including carton label artwork as part of a continuous effort to improve the organization and clarity of the SureClick Autoinjector (AI) instructions. Subsequently, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Repatha Instructions for Use (IFU) and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS CONSIDERED

This section lists the materials considered for our review of BLA 125522/S-045.

| Table 1. Materials Considered for this Review | |
|---|---|
| Materials Considered | Appendix Section |
| Relevant Product Information | A |
| Labels and Labeling | B |
| Previous DMEPA Reviews | C |

## 3 CONCLUSION

We evaluated the proposed Repatha Instructions for Use (IFU) and determined that it is acceptable from a medication error perspective.

However, the proposed Repatha carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Amgen Inc in Section 4.

Note that DMEPA is evaluating the HF validation study results under separate cover and, based on the outcome of that review, additional label and labeling comments may be forthcoming.

## 4 RECOMMENDATIONS FOR AMGEN INC

A. Carton Labeling

1. As currently presented, product information is duplicated between the PDP and back panel. We reserve the PDP for the most important warnings and caution statements. Consider deleting the following statements and accompanying graphics to reduce clutter on the PDP since this information is already presented on the back panel:

    a. “Caution, See package insert for full prescribing information and Instructions for Use”.

    b. “Do Not Re-use”

c. “This product contains dry natural rubber”

d. “Refrigerate until ready to use”

2. As currently presented the route of administration lacks prominence. Inadequate legibility of important information like the route of administration may lead to confusion during administration of the medical product, which can lead to medication errors. We recommend improving the legibility of the route of administration. You could consider utilizing a larger font size or heavier type or other means to achieve this. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

3. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

4. We note that your previously approved 140 mg/mL autoinjector (AI) two-pack carton labeling included an image of two AIs, which helped differentiate the labeling from your 140 mg/mL AI one-pack carton labeling. To increase differentiation and help prevent product selection errors, we recommend including the previously approved image of two AIs.

5. (b) (4) Revise the net quantity statement to read “1 Prefilled Autoinjector” and “2 Prefilled Autoinjectors” on the one-pack and two-pack, respectively.

6. The machine readable (2D data matrix barcode) product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a

transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Repatha[a] received on December 19, 2024 from Amgen Inc.

| Table 2. Relevant Product Information for Repatha | |
|---|---|
| Initial Approval Date | August 27, 2015 |
| Proper Name | evolocumab |
| Indication | • To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults with established cardiovascular disease.<br>• as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C<br>• as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C<br>• as an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C |
| Dosage Form | injection |
| Strength | Prefilled syringe: 140 mg/mL<br>Autoinjector: 140 mg/mL<br>On-body infusor with prefilled cartridge: 420 mg/3.5 mL |
| Route of Administration | subcutaneous |

[a] Repatha [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Nov 2024. [cited 2025 Jan 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125522s044lbl.pdf.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Repatha</th></tr>
<tr><td>Dose and Frequency</td><td>
<ul>
<li>In adults with established cardiovascular disease or with primary hyperlipidemia:
<ul>
<li>The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously [see Dosage and Administration.</li>
<li>If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.</li>
</ul></li>
<li>In pediatric patients aged 10 years and older with HeFH:
<ul>
<li>The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously [see Dosage and Administration.</li>
<li>If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.</li>
</ul></li>
<li>In adults and pediatric patients aged 10 years and older with HoFH:
<ul>
<li>The initial recommended dosage of REPATHA is 420 mg once monthly administered subcutaneously [see Dosage and Administration.</li>
<li>The dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks.</li>
<li>Patients on lipid apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule. Administer REPATHA after the apheresis session is complete.</li>
</ul></li>
</ul>
</td></tr>
<tr><td>How Supplied</td><td>
Not Made with Natural Rubber Latex –
<table>
<tr><td>140 mg/mL prefilled single-dose SureClick® autoinjector</td><td>2 pack</td><td>NDC 72511-393-02</td></tr>
<tr><td>140 mg/mL prefilled single-dose SureClick® autoinjector</td><td>1 pack</td><td>NDC 72511-393-01</td></tr>
<tr><td>140 mg/mL prefilled single-dose Syringe</td><td>1 pack</td><td>NDC 72511-501-01</td></tr>
<tr><td>420 mg/3.5 mL single-dose Pushtronex® system (on-body infusor with prefilled cartridge)</td><td>1 pack</td><td>NDC 72511-770-01</td></tr>
</table>
Contains Dry Natural Rubber –
<table>
<tr><td>140 mg/mL prefilled single-dose SureClick® autoinjector*</td><td>2 pack</td><td>NDC 72511-760-02</td></tr>
<tr><td>140 mg/mL prefilled single-dose Syringe*</td><td>1 pack</td><td>NDC 72511-750-01</td></tr>
</table>
* The needle cover of the glass prefilled single-dose SureClick® autoinjector and prefilled single-dose syringe contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex [see Warnings and Precautions (5.1)].
</td></tr>
<tr><td>Storage</td><td>Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.<br><br>For convenience, REPATHA may be kept at room temperature at 68°F to 77°F (20°C to 25°C) in the original carton for 30 days. If not used within the 30 days, discard REPATHA.</td></tr>
</table>

| Table 2. Relevant Product Information for Repatha | |
|---|---|
| Container Closure | SureClick autoinjector, prefilled syringe, and Pushtronex system (on-body infusor with prefilled cartridge) |

## APPENDIX B. LABELS AND LABELING

### B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Repatha labels and labeling submitted by Amgen Inc.

- Instructions for Use received on December 19, 2024, available from \\CDSESUB1\EVSPROD\bla125522\0395\m1\us\114-labeling\draft\labeling\d-repatha-dry-natural-rubber-ai-ifu-vxx-c-2024-1219.pdf.
- Carton labeling received on December 19, 2024
- Professional Sample Carton Labeling received on December 19, 2024

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B.2 Carton Labeling Images

Carton Labeling:

(b) (4)

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## APPENDIX C. PREVIOUS DMEPA REVIEWS

On March 13, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, "Repatha". Our search identified one previous review[c] since the date of our last search on August 07, 2024, and we considered our previous recommendations to see if they are applicable for this current review.

[c] Owens, L. Label and Labeling Review for Repatha (BLA 125522/S-044). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Aug 19. TTT ID No.: 2024-9823.

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DAMON A BIRKEMEIER
05/20/2025 02:46:01 PM

IDALIA E RYCHLIK
05/20/2025 04:13:20 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125522Orig1s045

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**From:** PickingIII, Ronald
**Sent:** Tue 10 Jun 2025 01:54:12 PM -0400 UTC
**To:** Ponnuru, Anusha
**Subject:** BLA 125522/S-045 Repatha, FDA labeling comments
**Attachments:** BLA 125522 S044 PPI with revisions.docx, BLA 125522 S045 Repatha AI Reference Guide.docx, BLA 125522 S045 Repatha latex AI IFU.docx, BLA 125522 S045 Repatha latex-free AI IFU.docx, BLA 125522 S044 PI with revisions.docx

Hi Anusha,

Please see the attached FDA labeling comments on the Repatha IFUs and reference guide for BLA 125522/S-045.

I've also included the Repatha PI and PPI that was approved with S-044 containing recommended updates. Please update any annual reportable changes that have been implemented since the approval of S-044 with your reply.

Additionally, we have the following comments on the carton labeling:

1. As currently presented, product information is duplicated between the PDP and back panel. We reserve the PDP for the most important warnings and caution statements. Consider deleting the following statements and accompanying graphics to reduce clutter on the PDP since this information is already presented on the back panel:
    a. "Caution, See package insert for full prescribing information and Instructions for Use".
    b. "Do Not Re-use"
    c. "Refrigerate until ready to use"
2. As currently presented the route of administration lacks prominence. Inadequate legibility of important information like the route of administration may lead to confusion during administration of the medical product, which can lead to medication errors. We recommend improving the legibility of the route of administration. You could consider utilizing a larger font size or heavier type or other means to achieve this. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

4. We note that your previously approved 140 mg/mL autoinjector (AI) two-pack carton labeling included an image of two AIs, which helped differentiate the labeling from your 140 mg/mL AI one-pack carton labeling. To increase differentiation and help prevent product selection errors, we recommend including the previously approved image of two AIs.
5. (b) (4) evise the net quantity statement to read "1 Prefilled Autoinjector" and "2 Prefilled Autoinjectors" on the one-pack and two-pack, respectively.
6. The machine readable (2D data matrix barcode) product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

Please accept all FDA edits with which you agree. The document that you return to us should only show in tracked changes: (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. If you do not agree with an FDA edit, add a comment bubble, that begins with "Applicant response to FDA change" or "Applicant comment."

We ask that you provide the revised labeling by **Tuesday, June 17**. The labeling can be sent to me via email and does not need to be submitted to the application until we have agreed-upon labeling.

We remind you that these edits do not reflect the final regulatory decision for this application.

Thanks,

Ron

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/s/

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RONALD D PICKING
06/11/2025 10:32:43 AM
See source file for attachments

## Mathew, Davis

**From:** Mathew, Davis
**Sent:** Thursday, April 10, 2025 3:32 PM
**To:** aponnuru@amgen.com
**Cc:** Rashid, Nichelle E; Joshi, Ameet; PickingIII, Ronald
**Subject:** BLA 125522 S-045 Repatha Human Factors Information Request

Dear Dr. Ponnuru,

Please refer to your supplemental biologics license application (sBLA) dated and received, December 19, 2024, under section 351(k) of the Public Health Service Act for Repatha (evolocumab) Injection.

We also refer to:

- Your December 19, 2024 submission, containing Human Factors /Usability Engineering (HF/UE) Summary Reports, labels, and labeling.
- Your submission, dated and received March 20, 2025, in response to our March 17, 2025, information request.

We are reviewing your submission and have the following information requests. We request a prompt response by **COB Monday, April 14, 2025**, in order to continue our evaluation of your submission.

With the currently submitted information, it is difficult from a review perspective to comprehensively review the human factors (HF) validation study results. To facilitate an efficient review, we request you provide the following information:

a. Moderator Script
b. Sequence of Study

The requested information should be submitted to BLA in eCTD Section 5.3.5.4- other Study reports and related information. We request a prompt response to the following inquiry within 48 hours of receiving this request in order to continue our evaluation of your submission.

Place your response in eCTD Section 5.3.5.4 – Other Study reports and related information.

Include the following statement "**RESPONSE TO HF INFORMATION REQUEST**" in bold capital letters at the top of your cover letter, and at the top of the first page of the main submission document.

Please submit a courtesy copy of your response via email followed by an official submission to your application.

If you have any questions regarding the contents of this letter or any other aspects of the Human Factors review process, contact me at (240) 402-4559.

Thank you,

**Davis Mathew, PharmD, RPh**
Safety Regulatory Project Manager
Center for Drug Evaluation and Research (CDER)

Office of Surveillance and Epidemiology (OSE)
**Ph:** 240-402-4559
**E:** davis.mathew@fda.hhs.gov

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/s/

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DAVIS MATHEW
04/10/2025 03:55:17 PM

**Mathew, Davis**

**From:** Mathew, Davis
**Sent:** Monday, March 17, 2025 11:27 AM
**To:** aponnuru@amgen.com
**Cc:** Rashid, Nichelle E; Joshi, Ameet
**Subject:** BLA 125522/S-045 Repatha Human Factors Information Request

Dear Dr. Ponnuru,

Please refer to your supplemental biologics license application (sBLA) dated and received, December 19, 2024, under section 351(k) of the Public Health Service Act for Repatha (evolocumab) Injection.

We also refer to your December 19, 2024 submission, containing Human Factors /Usability Engineering (HF/UE) Summary Reports, labels, and labeling.

We are reviewing your submission and have the following information requests. We request a prompt response by **COB Wednesday, March 19, 2025**, in order to continue our evaluation of your submission.

> Per the cover letter submitted on December 19, 2024 for Repatha, the aforementioned submissions are intended to harmonize the Instructions of Use (IFU), Reference Guide (RG), and secondary packaging (i.e. carton labeling and tray labeling) across Aimovig, Repatha, and Enbrel as part of the continuous effort to harmonize the IFU across multiple Amgen products that use the SureClick Autoinjector device platform.

1. It is unclear what the differences are between the currently marketed and the proposed device label, carton labeling, IFU, and RG for each product. Therefore, we request you submit the following:
    a. A separate side-by-side comparison for each product comparing the currently marketed Aimovig, Repatha, or Enbrel IFU and RG to the clean version with the proposed changes implemented of the Aimovig, Repatha, or Enbrel IFU and RG submitted on December 19, 2024 highlighting the changes.
    b. A separate side-by-side comparison for each product comparing the currently marketed Aimovig, Repatha, or Enbrel carton labeling and device tray labeling as compared to the proposed Aimovig, Repatha or Enbrel carton labeling and device tray labeling submitted on December 19,2024 highlighting the changes.

c. Confirm if you are proposing any changes to the currently marketed container labels (i.e., device labels) for Aimovig, Repatha, and/or Enbrel. If yes, submit:
    i. The proposed container labels.
    ii. A side-by-side comparison of the currently marketed container label and the proposed container label highlighting the differences.

2. It is unclear what the differences are between the proposed labeling among all the three products, Aimovig, Enbrel, and Repatha. Therefore, we request you submit the following:
    a. A single side-by-side comparison of the proposed IFU and RG for Aimovig, Repatha, and Enbrel highlighting the differences among the three products.

3. We acknowledge the submission of separate HF/UE Summary Reports for Aimovig BLA761077/S-025, Enbrel BLA 103795/S-5603, and Repatha BLA 125522/S-4 supplements. We note that performance data for the same participants are included in multiple reports. For example, all 3 reports include the same use error performed by participant CBN03 for task 5.1 "User properly removes cap from SC device just before injection." Since the intention is to only harmonize the IFU, RG, carton labeling, and tray labeling across multiple Amgen products at this time, a separate Human Factors Validation Study (HFVS) performance data for each product is not necessary. Thus, we would, in this instance, recommend submitting a single summary performance data table for all three products tested.

See the example below of how to present the requested information above in a single performance table (not-all inclusive):

**Table of Performance Data Across All Three Products (Aimovig, Enbrel, and Repatha)**

| Task | Total Use Errors Across All Three Products | Study participant's subjective feedback | Root Cause analysis | Mitigation Strategies |
|---|---|---|---|---|
| 4.2 User inspects carton for damage and tampering | **Total Success (n= total number of successes across all 3 products)**<br><br>**Total success with close call or use difficulties (n=1) DBN03**<br><br>One (1) participant **(DBN03)** initially provided partially | **DBN03** had a difficulty. When asked by the moderator if there was a physical way to know the car- ton was tampered with, the participant mentioned a tamper- ed seal and expiration date. | Carton information **(DBN03)**: There was no information on the carton to instruct the user to check the seal before use.<br><br>Study artifact/ Confusing question **(DN03)**: The intent | UI - Carton Labeling – Text communicates that product should not be used if carton seal is broken.<br><br>UI - Labeling IFU - Text communicates that product should not be used if carton is damaged or the carton seal is broken. |

| | | | | |
|---|---|---|---|---|
| | correct answer but was able to correct.<br><br>**Total Use Errors (n=1) AAN07**<br><br>One (1) participant **(AAN07)** did not understand the question and was under the impression that the answer will be provided on the carton. | | of the question was unclear. | Critical knowledge is confirmed and no additional modification to the product UI are necessary.<br><br>Residual risk was evaluated through the risk management process and found to be acceptable without further modifications to the UI. |
| | | **AAN07** focused on the indications listed on the back of the carton expecting to find a specific answer. | Study artifact/ Confusing question **(AAN07)**: The intent of the question was unclear. | |

Place your response in eCTD Section 5.3.5.4 – Other Study reports and related information.

Include the following statement "**RESPONSE TO HF INFORMATION REQUEST**" in bold capital letters at the top of your cover letter, and at the top of the first page of the main submission document.

Please submit a courtesy copy of your response via email followed by an official submission to your application.

If you have any questions regarding the contents of this letter or any other aspects of the Human Factors review process, contact me at (240) 402-4559.

Thank you,

**Davis Mathew, PharmD, RPh**
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
**Ph**: 240-402-4559
**E**: davis.mathew@fda.hhs.gov

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/s/

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DAVIS MATHEW
03/17/2025 11:42:45 AM

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

# REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

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

| TO: | FROM: (Name/Title, Office/Division/Phone number of requestor) |
|---|---|
| **CDER-OPDP-RPM** | Ron Picking RPM DRO-CHEN for DDLO 240-402-3211 |

| REQUEST DATE: | IND NO. | BLA NO. | TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) |
|---|---|---|---|
| 1/8/2025 | | 125522/S-045 | |

| NAME OF DRUG: | PRIORITY CONSIDERATION: | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) |
|---|---|---|---|
| Repatha (evolocumab) injection | Standard | PCSK9 mAb | May 21, 2025 |

| NAME OF FIRM: | |
|---|---|
| Amgen, Inc. | PDUFA Date: June 19, 2025 |

## TYPE OF LABEL TO REVIEW

**TYPE OF LABELING:**
**(Check all that apply)**
☐ PRESCRIBING INFORMATION (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☒ INSTRUCTIONS FOR USE(IFU)

**TYPE OF APPLICATION/SUBMISSION**
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ PLR CONVERSION

**REASON FOR LABELING CONSULT**
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

**For OSE USE ONLY**
☐ REMS

**EDR link to submission:**
**EDR Location: \\CDSESUB1\evsprod\BLA125522\0395**

**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.**

**OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.**

**COMMENTS/SPECIAL INSTRUCTIONS:**

Amgen submitted S-045 to BLA 125522 on December 19, 2024 to update the Repatha SureClick autoinjector IFUs (latex-containing and latex-free), reference guide, and carton labeling to improve clarity of instructions.

Review Team
Clinical: Ginger Winston/Eileen Craig
ADL: Melinda Wilson

OPQ: Wayne Seifert/Zhong Li
OSE: TBD
RPM: Ron Picking/Liz Solomon

SIGNATURE OF REQUESTER
Ron Picking

| SIGNATURE OF RECEIVER | METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND |
|---|---|

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RONALD D PICKING
01/08/2025 05:00:05 PM

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)

Ron Picking RPM DRO-CHEN for DDLO 240-402-3211

REQUEST DATE:

1/8/2025

BLA NO.:

125522/S-045

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:

Repatha (evolocumab) injection

PRIORITY CONSIDERATION:

Standard

CLASSIFICATION OF DRUG:

PCSK9 mAb

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

May 21, 2025

SPONSOR:

Amgen, Inc.

PDUFA Date: June 19, 2025

## TYPE OF LABEL TO REVIEW

**TYPE OF LABELING:**
**(Check all that apply)**
☐ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☒ INSTRUCTIONS FOR USE(IFU)

**TYPE OF APPLICATION/SUBMISSION**
☐ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

**REASON FOR LABELING CONSULT**
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

**EDR link to submission:**

**EDR Location: \\CDSESUB1\evsprod\BLA125522\0395**

**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.**

**COMMENTS/SPECIAL INSTRUCTIONS:**

Amgen submitted S-045 to BLA 125522 on December 19, 2024 to update the Repatha SureClick autoinjector IFUs (latex-containing and latex-free), reference guide, and carton labeling to improve clarity of instructions.

Review Team
Clinical: Ginger Winston/Eileen Craig
ADL: Melinda Wilson
OPQ: Wayne Seifert/Zhong Li
OSE: TBD
RPM: Ron Picking/Liz Solomon

SIGNATURE OF REQUESTER

| Ron Picking | |
|---|---|
| SIGNATURE OF RECEIVER | |

Version: 06/06/2016

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RONALD D PICKING
01/08/2025 05:03:16 PM

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

# REQUEST FOR CONSULTATION

| | | | | |
|---|---|---|---|---|
| TO *(Division/Office)*: **Mail: OSE** | | | FROM: Ron Picking RPM DRO-CHEN for DDLO 240-402-3211 | |
| DATE: January 7, 2025 | IND NO. | BLA NO.: 125522/S-045 | TYPE OF DOCUMENT: Labeling supplement – Labeling and HF reports | DATE OF DOCUMENT: December 19, 2024 |
| NAME OF DRUG: Repatha (evolocumab) injection | PRIORITY CONSIDERATION: Standard | | CLASSIFICATION OF DRUG: PCSK9 mAb | DESIRED COMPLETION DATE: April 30, 2025 |
| NAME OF FIRM: Amgen, Inc. | | | | |

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- X OTHER *(SPECIFY BELOW)*:

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

Amgen submitted S-045 to BLA 125522 on December 19, 2024 to update the Repatha SureClick autoinjector IFUs (latex-containing and latex-free), reference guide, and carton labeling to improve clarity of instructions. The submission also includes a URRA and a Human Factors report. We are consulting OSE for review of these reports and the updated labeling.

EDR Location: \\CDSESUB1\evsprod\BLA125522\0395

Tracked changes IFU and RG labels are on the DDLO sharepoint at the link below, carton labeling is in PDF in the EDR link.

S045 labeling

Review Team
Clinical: Ginger Winston/Eileen Craig
ADL: Melinda Wilson
OPQ: Wayne Seifert/Zhong Li
RPM: Ron Picking/Liz Solomon

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check all that apply) |
|---|---|
| Ron Picking | ☐ MAIL X DARRTS ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

06/18/2013

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/s/

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RONALD D PICKING
01/07/2025 04:29:04 PM

BLA 125522/S-045

**ACKNOWLEDGMENT --**
**PRIOR APPROVAL SUPPLEMENT**

Amgen Inc.
Attention: Anusha Ponnuru, PharmD
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Ponnuru:

We have received your supplemental biologics license application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

**BLA NUMBER:** 125522

**SUPPLEMENT NUMBER:** S-045

**PRODUCT NAME:** Repatha (evolocumab) injection

**DATE OF SUBMISSION:** December 19, 2024

**DATE OF RECEIPT:** December 19, 2024

This supplemental application proposes changes to the Repatha SureClick autoinjector Instructions for Use, Reference Guide, and carton labeling to improve organization and clarity of instructions.

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 **February 17, 2025**, in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be **June 19, 2025**.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

If you have questions, call me at 240-402-3211.

Sincerely,

*{See appended electronic signature page}*

Ron Picking, Pharm.D.
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology,
Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

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RONALD D PICKING
01/07/2025 03:33:56 PM