**BRAND NAME:** REPATHA

**PROPER NAME:** Evolocumab

**MANUFACTURER:** Amgen, Inc.

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

- to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.
- As an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).
- As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

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

**BLA NO:** 125522

**REGULATORY MILESTONES:**

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| **US pre-BLA** | April 10, 2014 |
| **US Approval** | August 27, 2015 |
| **EU Approval** | July 17, 2015 |
| **Health Canada Approval** | September 15, 2015 |
| **Japanese Ministry of Health, Labor and Welfare (MHLW) Approval** | January 21, 2016 |
| **TGA** | August 2 2018 |

**ADVISORY COMMITTEE:**

This BLA was discussed with the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 10 June 2015. The committee was asked to discuss the safety of evolocumab as observed in the clinical development program, to which the general consensus was that there were no serious safety signals observed with evolocumab treatment at this time. The committee was separately asked whether the applicant has sufficiently established that the LDL-Clowering benefit of evolocumab exceeds its risks to support approval for HoFH. The committee voted unanimously for approval. In their comments, several members stated that there is not enough evidence to suggest that the 420 mg Q2W dosage is more effective than 420 mg QM, but others stated that the potential benefit of more frequent dosing in this patient population outweighs any risk.

**MANUFACTURING:**

| PARAMETER | DATA | REFERENCE |
|---|---|---|
| **Manufacturer** | Amgen, Inc. | |
| **Indication** | REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated: | 1 |

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| | • to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.<br>• As an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).<br>• As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. | |
| **Cell Substrate** | Human monoclonal antibody (mAb; IgG2) | 3 |
| **Manufacturing platform** | The manufacture of evolocumab active substance represents a conventional monoclonal antibody production process (fermentation, recovery, purification, and viral inactivation/removal steps). | 3 |
| **Dose in vial/final container** | • Injection: 140 mg/mL solution in a single-use prefilled syringe<br>• Injection: 140 mg/mL solution in a single-use prefilled SureClick® autoinjector<br>• Injection: 420 mg/3.5 mL solution in a single-use Pushtronex® system (on-body infusor with prefilled cartridge) | 1 |
| **Dose to patient** | • Adults with established CVS disease or primary hyperlipidemia: 140 mg every 2 weeks or 420 mg once monthly.<br>• HoFH: 420 mg once monthly. | 1 |

1. Package insert - REPATHA
2. EPAR full - REPATHA
3. EPAR quality - Repatha: EPAR - Public assessment report
4. FDA Review - Repatha (evolocumab) injection

**CLINICAL TRIALS:**

| NCT | TRIAL PHASE | NO OF PATIENTS ENROLLED | TITLE | COUNTRIES |
|---|---|---|---|---|
| ***PHASE 2: Primary Hyperlipidemia and Mixed Dyslipidemia*** | | | | |
| NCT01375777 | 2 | 411 | Monoclonal Antibody Against PCSK9 to Reduce Elevated Low-density Lipoprotein Cholesterol (LDL-C) in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels | United States, Australia, Belgium, Canada, Denmark |
| NCT01380730 | 2 | 631 | LAPLACE-TIMI 57: Low-density Lipoprotein Cholesterol (LDL-C) Assessment with PCSK9 monoclonal Antibody Inhibition Combined with Statin therapy | United States, Canada, Czechia, Denmark, Hungary |
| NCT01375751 | 2 | 168 | Reduction of Low-Density Lipoprotein Cholesterol (LDL-C) with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study | |
| NCT01375764 | 2 | 160 | Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects | United States, Spain, Australia, Belgium, Canada, Denmark, Finland, Sweden |
| NCT01652703 | 2 | 310 | A Study to Evaluate Tolerability and Efficacy of Evolocumab (AMG 145) in Japanese Subjects | Japan |
| NCT01439880 | 2 | 1324 | Open Label Study of Long-Term Evaluation Against LDL-C Trial | United States, Australia, Belgium, Canada, South Africa, Czechia, Japan, Denmark, Finland, Spain, Germany, Hungary, Hong Kong, Norway, Netherlands, Singapore, |

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| | | | | Sweden, United Kingdom |
| ***Phase 3*** | | | | |
| NCT01763827 | 3 | 615 | Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2 | United States, Australia, Belgium, Canada, Denmark, France, Korea, Republic of, South Africa, Taiwan, Turkey |
| NCT01763866 | 3 | 2067 | LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy-2 | United States, Australia, Belgium, Canada, Hong Kong, France, Czechia, Denmark, Germany, Italy, Hungary, Korea, Republic of, Mexico, Netherlands, Russian Federation, Spain, South Africa, Sweden, Taiwan, Switzerland, United Kingdom |
| NCT01763905 | 3 | 307 | Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects -2 | United States, Australia, Belgium, Canada, Hong Kong, Denmark, France, Germany, Netherlands, Poland, South Africa, Spain, Switzerland, United Kingdom |
| NCT01763918 | 3 | 331 | Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2 | United States, Australia, Canada, France, Hong Kong, Germany, New Zealand, Netherlands, Norway, South Africa, Spain, Sweden, United Kingdom, Switzerland |
| NCT01879319 | 3 | 164 | Study to Assess in Home Use of Evolocumab (AMG 145) Administration Using Either an Automated Mini-doser or a Prefilled Autoinjector/Pen | United States, Canada |

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| NCT01849497 | 3 | 149 | Study to Assess In-home Use of Evolocumab (AMG 145) Using a Prefilled Syringe or a Prefilled Autoinjector/Pen | United States, Canada |
| NCT01516879 | 3 | 905 | Durable Effect of PCSK9 Antibody Compared with placebo Study | United States, Australia, Austria, Belgium, Canada, Czechia, Denmark, Hungary, South Africa |
| NCT01854918 | 3 | 3681 | Open-label Extension Study of Evolocumab (AMG 145) in Adults with Hyperlipidemia and Mixed Dyslipidemia | United States, Australia, Austria, Belgium, Hong Kong, Canada, Czechia, Denmark, France, Italy, Germany, Hungary, Japan, Korea, Republic of, Netherlands, New Zealand, Norway, Spain, Poland, South Africa, Taiwan Russian Federation, Sweden, Switzerland, United Kingdom |
| ***PHASE 2: HoFH*** | | | | |
| NCT01588496 | 2, 3 | 58 | Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities | United States, Belgium, Canada, Czechia, France, Hong Gong, Italy, Spain, New Zealand, Lebanon, Netherlands, South Africa, |
| ***PHASE 2/3: HoFH and "Severe" HoFH*** | | | | |
| NCT01624142 | 2, 3 | 300 | Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders | United States, Australia, Belgium, Brazil, Canada, Czechia, France, Greece, Hong Kong, Israel, Italy, Japan, Lebanon, New Zealand, Netherlands, South Africa, Spain, United Kingdom |

**POST APPROVAL CHANGES**

| DATE | TYPE OF CHANGE | DESCRIPTION | LINK |
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