Amgen Receives Positive CHMP Opinion Recognizing That Repatha® (evolocumab) Prevents Heart Attacks And Strokes

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Recommended Label Includes New Indication Based on the Repatha Cardiovascular Outcomes Study (FOURIER)
Amgen Continues to Work Closely With Payers on a Country-by-Country Basis to Ensure Access to Repatha for High-Risk Cardiovascular Patients

THOUSAND OAKS, Calif., March 23, 2018 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion to include a new indication in the Repatha® (evolocumab) label for adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels. The recommended label recognizes the positive findings from the Repatha cardiovascular outcomes study (FOURIER) and includes data on the additional reduction and prevention of heart attacks, strokes and coronary revascularizations on top of maximally tolerated statin therapy.

The Repatha cardiovascular outcomes study showed reductions in the risk of heart attack by 27 percent, the risk of stroke by 21 percent and the risk of coronary revascularization procedures by 22 percent in patients treated with Repatha and statin therapy compared to patients treated with placebo and statin therapy over a mean duration of 26 months.

"We welcome the CHMP's positive opinion to incorporate a new indication for adults with cardiovascular disease into the European label, recognizing the impact of Repatha to prevent life-changing events such as heart attacks and strokes," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "With the FOURIER outcomes data now included in the U.S. label and an anticipated label update in Europe in the coming months, we will continue to work with payers globally to ensure access to medication for higher-risk patients. Furthermore, we value and support the efforts by many stakeholders, including clinicians, advocates and payers, as we all work to reduce barriers to access and increase affordability for patients who need PCSK9 treatment."

The CHMP's positive opinion will now be reviewed by the European Commission (EC), which has the authority to approve medicines for the European Union (EU). If approved, the centralized European marketing authorization for Repatha will be updated to include the new indication. Norway, Iceland and Liechtenstein, as members of the European Economic Area (EEA), will take corresponding decisions on the basis of the EC's decision.

On Dec. 1, 2017, the U.S. Food and Drug Administration (FDA) approved a new indication for Repatha as the first PCSK9 inhibitor to prevent heart attacks, strokes and coronary revascularizations in adults with established cardiovascular disease following a priority review of Amgen's supplemental Biologics License Application.

Repatha Cardiovascular Outcomes (FOURIER) Study: Key Outcomes
The 27,564-patient Repatha cardiovascular outcomes study (FOURIER) demonstrated that adding Repatha to optimized statin therapy resulted in a statistically significant 20 percent (p<0.001) reduction in major adverse cardiovascular events (MACE) represented in the key secondary composite endpoint of time to first heart attack, stroke or cardiovascular death. The study found a statistically significant 15 percent reduction (p<0.001) in the risk of the primary composite endpoint, which included hospitalization for unstable angina, coronary revascularization, heart attack, stroke or cardiovascular death.

The magnitude of risk reduction in both the primary and key secondary composite endpoints grew over time, with the robust benefit starting as early as six months and accruing through the median 2.2 years of the study.

Patients on Repatha experienced a reduction in the risk of heart attack (27 percent, nominal p<0.001), stroke (21 percent, nominal p=0.01) and coronary revascularization (22 percent, nominal p<0.001).[1] Consistent with recent trials of more intensive LDL-C lowering, there was no observed effect on cardiovascular mortality. Similarly, there was no observed effect on hospitalization for unstable angina.[2-6]

The safety profile of Repatha in the outcomes trial was generally consistent with the safety profile for the 12- and 52-week controlled trials involving patients with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).

Repatha Cardiovascular Outcomes (FOURIER) Study Design
FOURIER (Further Cardiovascular OUTcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), a multinational Phase 3 randomized, double-blind, placebo-controlled trial, is designed to evaluate whether treatment with Repatha in combination with high- or moderate-intensity statin therapy compared to placebo plus statin therapy reduces cardiovascular events. The hard MACE composite endpoint is the time to cardiovascular death, myocardial infarction or stroke (key secondary endpoint). The extended MACE composite endpoint is the time to cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina or coronary revascularization (primary endpoint).

Eligible patients with high cholesterol (LDL-C ≥70 mg/dL or non-high-density lipoprotein cholesterol [non-HDL-C] ≥100 mg/dL) and established cardiovascular disease at more than 1,300 study locations around the world were randomized to receive Repatha subcutaneous 140 mg every two weeks or 420 mg monthly plus high- or moderate-intensity effective statin dose; or placebo subcutaneous every two weeks or monthly plus high- to moderate-intensity statin dose. Statin therapy was defined in the protocol as at least atorvastatin 20 mg or equivalent daily with a recommendation for at least atorvastatin 40 mg or equivalent daily where approved. The study was event driven and continued until at least 1,630 patients experienced a key secondary endpoint.

About Repatha® (evolocumab)
Repatha® (evolocumab) is a human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). Repatha binds to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, Repatha increases the number of LDLRs

available to clear LDL from the blood, thereby lowering LDL-C levels.[7]

Repatha is approved in more than 60 countries, including the U.S., Japan, Canada, and in all 28 countries that are members of the European Union. Applications in other countries are pending.

Important EU Product Information

In Europe Repatha is approved for use in:

Hypercholesterolemia and mixed dyslipidemia
Repatha is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolemia
Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia in combination with other lipid-lowering therapies.

Posology

Primary hypercholesterolaemia and mixed dyslipidaemia in adults
The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over
The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up-titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule.

Important Safety Information
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions: Renal impairment: Patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m^2) have not been studied. Repatha should be used with caution in patients with severe renal impairment. Hepatic impairment: In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDLC reduction. Therefore, close monitoring may be warranted in these patients. Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Repatha- should be used with caution in patients with severe hepatic impairment. Dry natural rubber: The needle cover of the glass pre-filled syringe and of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause allergic reactions. Sodium content: Repatha contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

Interactions: No formal drug-drug interaction studies have been conducted for Repatha. No studies on pharmacokinetic and pharmacodynamics interaction between Repatha and lipid-lowering drugs other than statins and ezetimibe have been conducted.

Fertility, Pregnancy and Lactation: There are no or limited amount of data from the use of Repatha in pregnant women. Repatha should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab. It is unknown whether evolocumab is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. No data on the effect of evolocumab on human fertility are available.

Undesirable Effects: The following common (≥ 1/100 to < 1/10) adverse reactions have been reported in pivotal, controlled clinical studies: influenza, nasopharyngitis, upper respiratory tract infection, rash, nausea, back pain, arthralgia, injection site reactions. Please consult the SmPC for a full description of undesirable effects.

Pharmaceutical Precautions: Store in a refrigerator (2 degrees C – 8 degrees C). Do not freeze. Keep the pre-filled syringe or the pre-filled pen in the original carton in order to protect from light. If removed from the refrigerator, Repatha may be stored at room temperature (up to 25 degrees C) in the original carton and must be used within 1 month.

Important U.S. Product Information

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 [HeFH]) 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.

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

patients with primary hyperlipidemia or HeFH.

Important U.S. Safety Information

Contraindication: Repatha is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha.

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

Adverse reactions: The most common adverse reactions (>5 percent of Repatha-treated patients and occurring more frequently than placebo) in controlled trials involving patients with primary hyperlipidemia, including HeFH, were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

In a 52-week trial, adverse reactions led to discontinuation of treatment in 2.2 percent of Repatha-treated patients and 1 percent 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 percent versus 0 percent for Repatha and placebo, respectively).

Adverse reactions from a pool of the 52-week trial and seven 12-week trials: Local injection site reactions occurred in 3.2 percent and 3.0 percent 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 percent and 0 percent, respectively.

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

The safety profile of Repatha in the cardiovascular outcomes trial was generally consistent with the safety profile in the 12- and 52-week controlled trials involving patients with primary hyperlipidemia, including HeFH. Serious adverse events occurred in 24.8 percent and 24.7 percent of Repatha-treated and placebo-treated patients, respectively. Adverse events led to discontinuation of study treatment in 4.4 percent of patients assigned to Repatha and 4.2 percent assigned to placebo. Common adverse reactions (>5 percent of patients treated with Repatha and occurring more frequently than placebo) included diabetes mellitus (8.8 percent Repatha, 8.2 percent placebo), nasopharyngitis (7.8 percent Repatha, 7.4 percent placebo) and upper respiratory tract infection (5.1 percent Repatha, 4.8 percent placebo). Among the 16,676 patients without diabetes mellitus at baseline, the incidence of new-onset diabetes mellitus during the trial was 8.1 percent in patients assigned to Repatha compared with 7.7 percent in those assigned to placebo.

Homozygous Familial Hypercholesterolemia (HoFH): In 49 patients with homozygous familial hypercholesterolemia studied in a 12-week, double-blind, randomized, placebo-controlled trial, 33 patients received 420 mg of Repatha subcutaneously once monthly. The adverse reactions that occurred in at least 2 (6.1 percent) Repatha-treated patients and more frequently than in placebo-treated patients, included upper respiratory tract infection (9.1 percent versus 6.3 percent), influenza (9.1 percent versus 0 percent), gastroenteritis (6.1 percent versus 0 percent), and nasopharyngitis (6.1 percent versus 0 percent).

Immunogenicity: Repatha is a human monoclonal antibody. As with all therapeutic proteins, there is a potential for immunogenicity with Repatha.

Please contact Amgen Medinfo at 800-77-AMGEN (800-772-6436) or 844-REPATHA (844-737-2842) regarding Repatha® availability or find more information, including full Prescribing Information, at www.amgen.com and www.Repatha.com.

About Amgen in the Cardiovascular Therapeutic Area
Building on more than three decades of experience in developing biotechnology medicines for patients with serious illnesses, Amgen is dedicated to addressing important scientific questions to advance care and improve the lives of patients with cardiovascular disease, the leading cause of morbidity and mortality worldwide.[8] Amgen's research into cardiovascular disease, and potential treatment options, is part of a growing competency at Amgen that utilizes human genetics to identify and validate certain drug targets. Through its own research and development efforts, as well as partnerships, Amgen is building a robust cardiovascular portfolio consisting of several approved and investigational molecules in an effort to address a number of today's important unmet patient needs, such as high cholesterol and heart failure.

About Amgen
Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Forward-Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products, including our devices, after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities, including in Puerto Rico, and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

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