Clinical Review of a PCSK9 Inhibitor in Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is associated with increased risk of secondary cardiovascular (CV) events, such as myocardial infarction (MI), stroke, and CV-related death. More than 25 years of evidence supports the linear relationship between the reduction of low-density lipoprotein cholesterol (LDL-C) and reduction in CV risk.

The American College of Cardiology and the American Heart Association have jointly issued guidelines on the management of blood cholesterol. High-intensity statin therapy or maximally tolerated statin therapy is recommended for patients with clinical ASCVD. Nonstatin medications, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, are considered for very high-risk ASCVD patients with elevated LDL-C (≥70 mg/dL) despite maximally tolerated statin therapy. Very high-risk ASCVD patients includes those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Additionally, patients who are unable to tolerate statin therapy because of adverse effects, such as statin-associated muscle symptoms, may benefit from a nonstatin medication.

PCSK9 INHIBITION WITH REPATHA® (EVOLOCUMAB)
Repatha® is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia, to reduce LDL-C. In adults with established CV disease, Repatha® is indicated to reduce the risk of MI, stroke, and coronary revascularization.

Mechanism of Action
Repatha® is a human monoclonal immunoglobulin G2 directed against human PCSK9. Repatha® binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDL-C receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. Repatha® increases the number of LDLRs available to clear LDL-C from the blood, thereby lowering LDL-C levels.

CLINICAL EFFICACY AND SAFETY OF REPATHA®
The Repatha® CV outcomes study (FOURIER) was a multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate CV risk reduction by dramatically lowering LDL-C in high-risk patients with established CVD, including patients with prior MI, prior stroke, or symptomatic peripheral arterial disease, with LDL-C ≥70 mg/dL and/or non-HDL-C ≥100 mg/dL. In addition to having background moderate- to high-intensity statin therapy, patients were randomized 1:1 to receive Repatha® 140 mg every 2 weeks or 420 mg once a month (n = 13,784) or placebo (n = 13,780); the median follow-up duration was 2.2 years.

Reduction in the Risk of CV Events
In the Repatha® CV Outcomes Study, high-risk patients with established CVD treated with Repatha® achieved significant reduction in the risk of the primary composite end point of time to CV events.

IMPORTANT SAFETY INFORMATION

- **Contraindication:** Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha®. Serious hypersensitivity reactions including angioedema have occurred in patients treated with Repatha®.

- **Allergic Reactions:** Hypersensitivity reactions (e.g. angioedema, 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 in Primary Hyperlipidemia (including HeFH):** The most common adverse reactions (>5% of patients treated with Repatha® and occurring more frequently than placebo) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

From a pool of the 52-week trial and seven 12-week trials: Local 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.

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

- **Adverse Reactions in the Cardiovascular Outcomes Trial:** The most common adverse reactions (>5% of patients treated with Repatha® and occurring more frequently than placebo) were: diabetes mellitus (8.8% Repatha®, 8.2% placebo), nasopharyngitis (7.8% Repatha®, 7.4% placebo), and upper

Please see additional Important Safety Information throughout.
death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (HR, 0.85; 95% CI, 0.79-0.92; P <0.0001). Repatha® demonstrated significant reduction in the risk of the key secondary composite end point of time to CV death, MI, or stroke by 20% compared with placebo (HR, 0.80; 95% CI, 0.73-0.88; P <0.0001), and the benefit improved over time in the study. The observed HR for CV death was 1.05 (95% CI, 0.88-1.25) and for hospitalizations due to unstable angina was 0.99 (95% CI, 0.82-1.18).

**LDL-C Reduction**

In the Repatha® CV Outcomes Study, at Week 12, Repatha® added to a statin demonstrated a 63% reduction in LDL-C (95% CI, 62-63) and 59% at Week 48 (95% CI, 58-60; P <0.001). Nearly 90% of patients treated with Repatha® added to a statin achieved LDL-C levels of 70 mg/dL or lower compared with 18% of patients in the placebo group (P <0.001) at Week 48.

**Safety**

In the Repatha® CV Outcomes Study, adverse reactions that occurred in more than 5% of patients treated with Repatha® and more frequently than with placebo included diabetes mellitus, nasopharyngitis, and upper respiratory tract infection. In EBBINGHAUS, a substudy of 1974 patients enrolled in the FOURIER trial, Repatha® was noninferior to placebo on selected cognitive function domains as assessed with the use of neuropsychological function tests over a median follow-up of 19 months.

**ROLE OF THE PHARMACIST**

As an integral part of the health care team, pharmacists are well suited to make interventions when it comes to gaps in care. For patients with established CVD with LDL-C levels ≥70 mg/dL, despite maximally tolerated statin therapy, the risk of another cardiovascular event remains. Pharmacists are able to recognize these types of patients and work with physicians to provide appropriate care.

Pharmacists play a key role in educating patients about the importance of medication adherence. They are able to explain to patients the importance of achieving low LDL-C levels in order to reduce the risk of a recurrent CV event. In addition, pharmacists are able to guide patients to maintain a healthy lifestyle (eg, diet, physical activity, avoiding tobacco use) in conjunction with medication use.

**REFERENCES**

4. Repatha® (evolocumab) prescribing information, Amgen.

**IMPORTANT SAFETY INFORMATION (continued)**

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 assigned to Repatha® compared with 7.7% in those assigned to placebo.

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

**INDICATIONS**

- **Prevention of Cardiovascular Events:** In adults with established cardiovascular disease, Repatha® is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization.

- **Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia):** Repatha® is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).

Please see additional Important Safety Information throughout and Brief Summary of Prescribing Information on the next page.

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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 372-week trials. The mean and median duration of treatment in these trials was 10 weeks and 12 weeks, respectively. Local Injection Site Reactions Injection site reaction rates in REPATHA-treated patients were 3.2% and 3.0% in 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 0.0%, respectively.

Adverse Reactions in the Cardiovascular Outcomes Trial
In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial (Study 1 [DESCARTES, NCT01740195]), 10,151 patients received at least one dose of REPATHA or placebo (see Clinical Studies [4.1]). The mean age group was 62.2 years (range: 13 to 57 years), 45% were 65 years or older, 13% were 75 years or older, 52% were women, 85% White, 2% Black, and 5% Asian; 6% identified as Hispanic ethnicity. Patients were exposed to REPATHA or placebo for a median of 134 months (range: 2 to 129 months). The proportions of patients who discontinued treatment due to adverse reactions were 11.5% in the 2-week REPATHA group and 10.2% in the placebo group. The adverse reactions that occurred in at least 2% of REPATHA-treated patients and more frequently than placebo were:

• Upper respiratory tract infection (9.3% vs 8.3%)
• Influenza (9.3% vs 8.3%)
• Gastroenteritis (8.1% vs 7.3%)
• Myalgia (8.1% vs 7.3%)

6.2 Immune Response
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, there may be differences in 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 electrochemiluminescence bridging single-analyte immunoassay (ECLIA). Antibody titers were determined using the ECLIA. For patients whose sera tested positive in the screening immunovirology, an in vitro bioassay was performed to confirm the antibody activity.

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

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

6.3 Postmarketing Experience
The following additional adverse reactions have been identified during postapproval use of REPATHA. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

• Allergic reactions: urticaria
• Urinary tract infection

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy registry that monitors pregnancy outcomes in women exposed to REPATHA during pregnancy. Please contact 1-877-311-9372 or (https://repatha.org) or (https://repatha.org) in or out to obtain information about the registry.

8.2 Lactation
Breastfeeding
There is no information regarding the presence of evolocumab in human milk; the effects on the breastfed infant or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REPATHA.

Lactation
There are no reports of evolocumab in human milk; the effects on the breastfed infant or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REPATHA. Patients should only breastfeed if the potential benefit justifies the potential risk to the fetus.