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Enlicitide: The first oral PCSK9 inhibitor approved for treatment of hypercholesterolemia

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SUMMARY: Hypercholesterolemia, and particularly elevated low-density lipoprotein cholesterol (LDL-C), is a major causal factor in atherosclerotic cardiovascular disease (ASCVD) and contributes substantially to coronary heart disease, ischemic stroke, and peripheral artery disease. Statins remain the cornerstone of lipid-lowering therapy, while ezetimibe and injectable proprotein convertase subtilisin/kexin 9 (PCSK9) targeted agents are added when further LDL-C reduction is required. However, concerns about injections, cost, accessibility, and treatment inertia have limited the use of existing PCSK9 therapies, creating a need for potent oral alternatives. Enlicitide, approved by the US Food and Drug Administration in July 2026, is the first approved oral PCSK9 inhibitor. This macrocyclic peptide blocks the interaction between circulating PCSK9 and hepatic LDL receptors, thereby increasing receptor recycling and LDL-C clearance. In the phase III CORALreef Lipids and CORALreef HeFH trials, once-daily enlicitide reduced LDL-C by approximately 60%, and the effect was maintained for up to 52 weeks. Adverse event rates were generally similar to those observed with a placebo. Nevertheless, those trials primarily evaluated LDL-C reduction rather than cardiovascular outcomes, and their duration was insufficient to establish long-term safety. The ongoing CORALreef Outcomes trial will determine whether enlicitide-mediated LDL-C reduction translates into fewer major cardiovascular events and will help define its long-term clinical role.

Keywords: PCSK9, LDL-C, LDLR, ASCVD, enlicitide

Hypercholesterolemia is a lipid metabolism disorder characterized primarily by elevated plasma total cholesterol, and low-density lipoprotein cholesterol (LDL-C) in particular. Cumulative exposure to LDL-C over time promotes lipid retention within the arterial intima, triggering inflammation and atherosclerotic plaque formation and ultimately increasing the risks of coronary heart disease, ischemic stroke, and peripheral artery disease (*1*). Genetic and epidemiological studies have established LDL as an important causal factor in atherosclerotic cardiovascular disease (ASCVD) (*2*). A study covering 200 countries showed that the global burden of cholesterol-related diseases is gradually shifting from high-income Western countries to East and Southeast Asia (*3*). In 2017, elevated non-high-density lipoprotein cholesterol (non-HDL-C) was responsible for approximately 3.9 million deaths, half of which occurred in East, Southeast, and South Asian countries (*3*).

Treatments for elevated LDL-C in patients with hypercholesterolemia should be individualized according to the overall risk of cardiovascular events (*4*). Dietary modifications, regular physical activity, weight management, and smoking cessation are the foundations of long-term management; however, most high-risk patients still require pharmacological treatment. Statins have robust evidence supporting their cardiovascular benefits and remain the cornerstone of lipid-lowering therapy (*5*). For patients who fail to achieve target LDL-C levels despite receiving a maximally tolerated statin dose, additional agents such as ezetimibe are generally recommended. For patients with very-high-risk ASCVD, heterozygous familial hypercholesterolemia (HeFH), or a need for substantial LDL-C reduction, early combination therapy incorporating a proprotein convertase subtilisin/kexin 9 (PCSK9) targeted agent should be considered (*6*).

Before the approval of enlicitide, all marketed therapies targeting PCSK9 were administered by injection. Alirocumab and evolocumab act by binding to circulating PCSK9, they reduce LDL-C levels by approximately 60%, and they have been found to decrease the incidence of cardiovascular events (*7,8*). Inclisiran, a small interfering RNA therapeutic, lowers LDL-C by suppressing PCSK9 synthesis in hepatocytes. It is administered once every six months and reduces LDL-C levels by approximately 50% (*9*). Despite

their potent lipid-lowering effects, these agents may be used to a limited extent clinically due to concerns about injections, cost, accessibility, and therapeutic inertia. Conversely, conventional oral non-statin agents generally do not provide a sufficient LDL-C reduction to meet the treatment needs of some high-risk patients. Therefore, an agent combining the convenience of oral administration with potent LDL-C-lowering efficacy has long represented an unmet clinical need.

On July 15, 2026, the US Food and Drug Administration approved enlicitide (trade name: LIPFENDRA) 20-mg tablets as an adjunct to diet and exercise to reduce LDL-C levels in adults with hypercholesterolemia, including those with HeFH. Enlicitide is the first oral PCSK9 inhibitor approved worldwide (*10,11*). It is a macrocyclic peptide that binds to circulating PCSK9 and blocks its interaction with the low-density lipoprotein receptor (LDLR) on the hepatocyte surface. This reduces LDLR degradation, allowing more receptors to be recycled to the hepatocyte surface and remove LDL-C from the circulation (*11,12*). Enlicitide tablets contain sodium caprate as an absorption enhancer, although their oral bioavailability remains only approximately 1%. The tablet must be swallowed whole in the morning on an empty stomach, and patients should wait at least 30 min after administration before eating. Its principal advantage is that it reduces LDL-C to a similar extent as PCSK9 monoclonal antibodies, albeit through oral administration, and it thereby represents a new option for patients who are unwilling or unable to receive long-term injectable therapy.

The approval of enlicitide was based primarily on two phase III randomized controlled trials. The CORALreef Lipids trial (NCT05952856) enrolled adults who had experienced an ASCVD event or were at risk of a first ASCVD event and who required further LDL-C reduction despite receiving stable lipid-lowering therapy (*13*). A total of 2,904 patients were included in the efficacy and safety analyses and were assigned in a ratio of 2:1 to receive enlicitide 20 mg or a placebo once daily for 52 weeks (*13*). At week 24, LDL-C levels had changed from the baseline by −57.1% in the enlicitide group and 3.0% in the placebo group, with an adjusted between-group difference of −55.8 percentage points. At week 52, the between-group difference remained −47.6 percentage points. The incidence of adverse events was comparable between the two groups (*13*). The CORALreef HeFH trial (NCT05952869) enrolled 303 adults with HeFH who were receiving stable moderate- or high-intensity statin therapy and randomly assigned them in a ratio of 2:1 to receive enlicitide or a placebo (*14*). At week 24, LDL-C levels had changed from the baseline by −58.2% and 2.6%, respectively, with a between-group difference of −59.4 percentage points (*14*). At week 52, the between-group difference was −61.5 percentage points, indicating that the lowering of LDL-C was sustained for one year. The incidence of adverse events was similar between the two groups (*14*).

The two studies consistently demonstrated the potent LDL-C-lowering efficacy of enlicitide; however, several limitations should be considered when interpreting their findings. First, the principal efficacy endpoint was the change in LDL-C rather than clinical outcomes such as myocardial infarction, stroke, or cardiovascular death. Second, a 52-week follow-up period is insufficient to evaluate efficacy over several years or to detect rare adverse events. The HeFH trial also had a relatively small sample size, and the high levels of adherence to the dosing and fasting requirements achieved in clinical trials may not be reproducible in routine clinical practice. Therefore, the available evidence supports the marked LDL-C-lowering efficacy of enlicitide but does not yet directly demonstrate that it reduces cardiovascular events.

The CORALreef Outcomes trial (NCT06008756) is currently underway. This phase III randomized, placebo-controlled trial involves approximately 14,550 adults at high cardiovascular risk and is designed primarily to determine whether enlicitide reduces the risk of a composite endpoint including coronary heart disease death, myocardial infarction, ischemic stroke, and major adverse limb events (*11,15*). The trial will determine whether the substantial LDL-C reduction achieved with enlicitide translates into fewer cardiovascular events in the future.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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