



**Indian Health Service**  
**National Pharmacy and Therapeutics Committee**  
**Formulary Brief: PCSK9 Inhibitors**  
- August 2017-



**Background:**

The IHS National Pharmacy & Therapeutics Committee (NPTC) discussed the PCSK9 Inhibitor class, including evolocumab and alirocumab, at the August 2017 meeting. Prior to the review, the National Core Formulary (NCF) included neither of these medications. After discussing the clinical data along with IHS procurement and utilization trends, **no modifications were made to the NCF.**

Having elevated total cholesterol levels approximately doubles the risk of heart disease, as excessive blood cholesterol levels can (along with other factors such as fatty substances, cellular waste products, calcium, and fibrin) cause build up on artery walls called plaques (atherosclerosis). Over 70 million adults in the United States have elevated low-density lipoprotein (LDL), and less than one-half are receiving treatment to reduce their LDL level (CDC, 2015). In 2015, the rate of cardiovascular disease (CVD) among American Indian / Alaska Natives was nearly twice that of the rest of the population (NHLBI 2015).

Available treatment options for hyperlipidemia include lifestyle modifications (eating a heart-healthy diet, limiting alcohol consumption, quitting tobacco usage, and increasing physical activity) and medications such as statins, fibrates, omega-3 fatty acid ethyl ester, niacin, bile-acid sequestrants, ezetimibe, and PCSK9 inhibitors (AHA, 2017).

**Discussion:**

The enzyme PCSK9 was identified in 2003 in families with autosomal dominant hypercholesterolemia (Joseph, 2017). It was determined to be the LDL receptor (LDL-R) regulator, found on chromosome 13. It is produced in the endoplasmic reticulum and modified in the Golgi apparatus, where it undergoes autocatalytic cleavage to enter the secretory pathway before being released into the circulation (Amritanshu, 2017). Most LDL particles are cleared from circulation by hepatic transmembrane LDL-Rs. The two particles bind, forming a complex which is then internalized via endocytosis. A pH decrease causes them to break apart, and the LDL-R returns to the cell membrane to repeat the cycle up to 150 times while the LDL particle is broken down to free cholesterol for storage or other cellular activities. PCSK9 decreases the LDL-R expression on the hepatocyte surface by binding to the extracellular domain of the LDL-R/LDL complex. This complex is then internalized and degraded by the lysosome, decreasing the number of receptors. Consequently, LDL clearance is decreased, leading to an increase in plasma LDL levels. PCSK9 inhibitors impede the binding of PCSK9 to LDL-R, which increases the number of receptors available to clear LDL and ultimately leads to lower LDL levels (Joseph, 2017; Lambert, 2012).

Evolocumab and alirocumab are PCSK9 inhibitors approved by the FDA in 2015 as an adjunct to maximally-tolerated statin doses for adults with heterozygous familial hypercholesterolemia (FH) or atherosclerotic CVD whose LDL is not adequately lowered. Evolocumab also has an indication for patients with homozygous FH on other lipid lowering therapy (Underberg 2017).

A 2017 Cochrane review evaluated PCSK9 inhibitors with the primary objective to quantify the short-term, medium-term, and long-term effects of PCSK9 inhibitors on lipids and CVD incidence. The authors also wanted to determine if the impact of PCSK9 inhibitor use varies between specific patient subgroups. They reviewed 20 studies with over 67,000 participants. The agents were compared to placebo, ezetimibe, or ezetimibe plus statins. All available data was from industry-funded trials, though there appeared to be a relatively low risk of bias. The findings concluded that PCSK9 inhibitors showed benefit in CV risk factors, decreased CV biomarkers (including LDL, apolipoprotein B, non-HDL cholesterol, triglycerides and lipoprotein a), and had protective effects against CVD events. There was minimal, if any, effect on all-cause mortality and a modest increase in adverse events. It is uncertain if the evidence supports usage for primary prevention, as most participants had established atherosclerotic CVD or were at high risk of CV events. Additionally, long-term data on efficacy and safety outcomes is unavailable. There was no apparent increased risk of cancer, but the largest trials did not provide cancer data.

Furthermore, while there appeared to be no increased risk for Type 2 Diabetes development, three recent large genetic studies with long-term follow up demonstrated that variation in the PCSK9 locus was associated with increased glucose and diabetes. Finally, high heterogeneity was observed in the biomarker response, indicating that personalized PCSK9 regimens may be more successful for optimal patient results (Schmidt, 2017).

A 2015 meta-analysis included 24 studies with over 24,000 participants comparing PCSK9 inhibitors to placebo or ezetimibe. Limitations included the usage of study-level data rather than patient-level data, that data was derived from a small number of events, broad ranges of duration of follow-up, and that patients were included with and without known genetic disorders. The authors found that the use of PCSK9 inhibitors was associated with lower odds of all-cause mortality and myocardial infarction, a statistically non-significant reduction in CV mortality, a small increase in serum creatinine kinase level, no increase in serious adverse events, and a profound reduction in lipid markers (Navarese, 2015).

The FOURIER trial compared evolocumab to placebo in 27,564 study participants with atherosclerotic CVD receiving statin therapy. Dramatic LDL lowering (59%,  $p < 0.001$ ) was observed out to 168 weeks and the primary endpoint of CV death, MI, stroke, hospitalization for unstable angina or coronary revascularization was reduced 15% (HR 0.85, 95% CI 0.79-0.92,  $p < 0.001$ ). No differences were noted between groups in all-cause mortality or adverse events, except injection-site reactions (Sabatine, 2017).

The 2016 European Society of Cardiology / European Atherosclerosis Society consensus statement added recommendations to consider PCSK9 Inhibitors in patients at very high cardiovascular risk and with defined LDL levels. Both the 2016 American College of Cardiology (expert consensus) and 2017 National Lipid Association recommendations include a place in therapy for PCSK9 inhibitors as adjunct agents.

#### Findings:

PCSK9 inhibitors can dramatically reduce LDL and other cardiovascular biomarkers, though mortality benefit has not been observed. Long-term data on efficacy and safety is as yet unavailable, and their utility is questionable in primary prevention. Meanwhile, statins are powerful lipid-lowering agents with proven mortality benefit that continue to be underutilized though relatively inexpensive. Based on these considerations, the NPTC declined to make changes to the NCF at this time.

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*If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).*

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