INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *PCSK9 Inhibitors*
-November 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors. The NPTC last reviewed hyperlipidemia in May 2022. The agents evaluated at the November 2024 meeting included evolocumab (Repatha®), alirocumab (Praluent®) and inclisiran (Leqvio®) for the treatment of hypercholesterolemia. Currently, the IHS National Core Formulary lists 4 statins (atorvastatin, pravastatin, rosuvastatin, simvastatin) and ezetimibe for the treatment of hypercholesterolemia. Following clinical review and analysis, the NPTC made **no modifications** to the National Core Formulary.

Atherosclerotic cardiovascular disease (ASCVD) is responsible for 1 in every 4 deaths in the United States and coronary heart disease (CHD) accounts for 34% of these deaths. Statins are first line pharmacologic therapy, targeting HMG CoA reductase to decrease cholesterol processing, upregulating LDL-receptors on the cell surface and increasing LDL clearance to reduce serum LDL levels. Ezetimibe prevents absorption of cholesterol from the small intestine. PCSK9 inhibitors act in the liver to prevent breakdown of the LDL receptor resulting in increased LDL receptor, higher clearance, and lower serum LDL.[2] Moreover, PCSK9 inhibitors have been shown to lower other markers of ASCVD such as CRP and Lp(a).[3] Evolocumab and alirocumab are monoclonal antibodies that target the PCSK9 enzyme, while inclisiran is a small molecule that silences the mRNA for the PCSK9 protein.[4] Evolocumab and alirocumab are both FDA approved for treatment of hypercholesterolemia in homozygous familial hypercholesterolemia (HoFH) and secondary prevention of ASCVD. Alirocumab also carries an indication for treatment for 'primary hyperlipidemia'. Inclisiran is FDA approved for the treatment of HoFH, heterozygous familial hypercholesterolemia (HeFH), secondary ASCVD, and primary prevention of ASCVD. Alirocumab may be used in pediatric patients ≥ 8 years old and evolocumab is approved for ages 12 and older.

Discussion:

Efficacy and Safety Data: *Primary Prevention*: All PCSK9 inhibitors are approved for treatment of primary prevention of ASCVD in patients with FH. Alirocumab and inclisiran carry indications for primary prevention of ASCVD in non-monogenic familial hypercholesterolemia. For patients with HoFH or HeFH, specialist consultation is recommended as treatments for these conditions should be initiated rapidly in conjunction with genetic testing.[7] Data for primary prevention with inclisiran for non-FH patients comes from the ORION-11 trial, showing that the placebo-corrected LDL-C change with inclisiran was -43.7% (95% CI: -52.8 to -34.6, p<0.0001). Inclisiran significantly lowered non-HDL cholesterol and apolipoprotein B (apoB) at Day 510 vs. placebo (p<0.0001 for both).[8] Inclisiran was well-and reduced ASCVD markers in patients without ASCVD however there were no outcomes data on morbidity and mortality. The FDA added primary prevention of ASCVD to approved indications based on this data. Alirocumab data for primary prevention comes from the ODESSEY trials which demonstrated a decrease in first events compared to placebo (by 190 cases out of 3,064) and reduced total risk of non-fatal CV events (HR 0.87; 95% CI: 0.82 to 0.93) and death (HR 0.83; 95% CI: 0.71 to 0.97).[9] All primary prevention data is time limited with longest interval of 540 days.

Secondary Prevention: Patients who have already had an ASCVD event are at high risk of having another event, and LDL lowering is key to prevention. The FOURIER trial compared evolocumab to standard lipid lowering therapy in patients with a history of ASCVD with LDL ≥70 mg/dL and demonstrated a 15% reduction in the risk of the primary composite end point (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) and a 20% reduction in the risk of the key secondary end points of cardiovascular death, myocardial infarction, or stroke with a number needed to treat (NNT) of 67 to prevent a major CV event.[10] The ODESSEY trial showed similar outcomes for alirocumab in secondary prevention favoring alirocumab treatment + usual care over placebo + usual care with a HR 0.85 (95% CI: 0.78 to 0.93; **p**<0.001) and a NNT of 62.5.[11] Post-hoc analysis of combined ODESSY data demonstrated a reduction in absolute risk of death with alirocumab and reduction in all-cause mortality in patients who achieved an LDL of ≤30 mg/dL.[11] ORION trials showed 50% reduction in LDL-C with inclisiran and 26% lower probability of MACE (OR 0.74; 95% CI: 0.58-0.94), however reductions in fatal and non-fatal MIs and strokes were not significant.[8] *Safety*: In all 3 aforementioned trials as well as meta-analyses reviewed, few serious AEs were reported with the most common being injection site reactions. Meta-analyses have not supported increased risk of sepsis, neurocognitive AEs, osteoporosis, or colonic tumors.[15-17]

Guidelines and Place in Therapy: Three guidelines were reviewed: European Society of Cardiology (ESC, 2021); American Academy of Clinical Endocrinology (AACE, 2020); and American Heart Association/American College of Cardiology (AHA/ACC, 2019). The summary of guidelines for primary prevention with regards to PCSK9 inhibitors: Statins remain first line. Inclisiran is FDA approved for primary prevention in non-FH hypercholesterolemia and should be used as a 3rd line agent to ezetimibe. PCSK9 inhibitors (mAbs and inclisiran) are second line treatment for primary prevention in any FH. Evolocumab and alirocumab seem to be more efficacious than inclisiran in patients with FH, however all are

efficacious in lowering LDL in FH patients but no outcomes data or long term data exist. For secondary prevention, guidelines agree that ezetimibe and PCSK9 inhibitors should be used as second line therapy to statins in very high risk patients. ESC guidelines do not differentiate between inclisiran and mAb-PCKS9 inhibitors, however ACC guidelines prefer mAb-PCKS9 inhibitors over inclisiran for the improved outcomes data. LDL goals are determined by 10-year ASCVD risk and comorbidities in patients with prior ASCVD events. AACE 2020 Guidelines provide excellent visual schematics. Patients with very high risk (10-year ASCVD risk >20%, recent ASCVD hospitalization, DM with one risk factor, CKD, or HeFH, e.g.) LDL goal is <70 mg/dL. For patients with extreme high risk for an ASCVD event (progressive ASCVD, established ASCVD with DM or CKD, premature ASCVD, e.g.) the goal is LDL <55 mg/dL.[18]

Clinical Use: Risk stratification is the initial step in choosing therapy for primary or secondary prevention of ASCVD. Currently the only validated ASCVD risk estimator is the AHA/ACC Risk Stratification Tool. While this tool has limitations, it is critical in decision algorithms for treatment plans including LDL goals and therapy choices.[5] As above, guidelines from the AACE, ESC, and AHA/ACC were reviewed. After risk stratification, a collaborative clinical discussion with a patient should include risk factor modification with lifestyle changes including weight loss, increased activity, diet modification, and treatment of comorbidities such as type II DM. Depending on risk and patient preference, **first line therapy for hypercholesterolemia in all circumstances is statin therapy, the intensity of which should be chosen based on risk stratification outcomes.** Additional risk stratification may be undertaken my measuring secondary biomarkers, such as Lp(a), hs-CRP, and apoB levels, interpretation of which may be aided by a cardiologist. Additional studies such as ankle-brachial index (ABI) or coronary artery calcium (CAC) score may also help to inform risk. Ultimately, if a patient needs pharmacologic treatment, the LDL goal will be determined by their risk category determined by the 10-year ASCVD risk and additional risk factors (refer to the AACE 2020 Guidelines for visual schematics of LDL goals). Once a patient has reached the maximally tolerated dose of statin with good adherence and has not reached their LDL goal, then additional therapy may be considered. Both ezetimibe and PCSK9 inhibitors have been shown to reduce LDL levels in addition to maximally tolerated statin, thus, unless the statin is not tolerated or otherwise contraindicated, it should be continued. As above, guidelines do not identify a preferred secondary agent, however, consideration of the degree of lipid lowering needed and patient preference may guide selection. Importantly, evolocumab and alirocumab are the only PCSK9 inhibitors with mortality benefits. Alirocumab is the only PCSK9 inhibitor that was shown to improve all-cause mortality. Ultimately, PCSK9 inhibitors may be considered where LDL is not well controlled and ASCVD risk is high, very high, or extremely high with cost consideration as a part of the non-formulary approval process, recognizing that preventing ASCVD events in appropriate high-risk patients prevents morbidity and mortality and is cost effective as a whole.[6]

Findings:

PCSK9 inhibitors are a safe and effective mechanism for lowering LDL cholesterol. Alirocumab and evolocumab improve morbidity and mortality in high-risk patients when used in addition to standard of care lipid lowering regimens. While ASCVD is common, AI/AN populations are at higher risk for ASCVD complications and death. The NCF currently carries effective first and second line treatments for these conditions (statins and ezetimibe). PSCK9 inhibitors are likely effective for a specific high-risk group of AI/AN patients.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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