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Indian Health Service National Pharmacy and Therapeutics Committee Dipeptidyl peptidase-4 (DPP-4) inhibitors NPTC Formulary Brief August Meeting 2017

Background:
The IHS National Pharmacy & Therapeutics Committee (NPTC) discussed the class of DPP-4 inhibitors at the August 2017 meeting. Currently, there are four approved DPP-4 inhibitors available in the U.S.; alogliptin (Nesina®), linagliptin (Tradjenta®), saxagliptin (Onglyza®) and sitagliptin (Januvia®). Prior to the review, the National Core Formulary (NCF) did not include any of the DPP-4 inhibitors. Based on the findings and following discussion of cost benefit analysis, the NPTC added saxagliptin to the NCF.

Dipeptidyl peptidase-4 inhibitors are a class of oral medications used to improve glycemic control in type 2 diabetes mellitus (T2DM). DDP-4 inhibitors act by preventing breakdown of incretins such as GLP-1 and GIP which promote endogenous insulin production and prevent secretion of glucose from the liver (suppression of glucagon) resulting in lower serum glucose and ultimately improved glycemic control.[1,2] FDA indications for DPP-4 inhibitors are as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (non-insulin dependent) as mono- or combo-therapy.[3] Notable warnings for this class include a recent FAERS database report indicating the increased incidence of severe and disabling joint pain. Other notable adverse events include bullous pemphigus, hypersensitivity reactions, exacerbation or development of CHF, and risk of renal impairment. Alogliptin alone carries a warning for risk of hepatic failure. All DPP-4 inhibitors are renally cleared (alogliptin both renal and hepatic) and are considered safe for use in renal patients at reduced doses. Notable drug-drug interactions include all CYP3A4 metabolized medications, use with other hypoglycemic agents, decreased efficacy of thiazide drugs with concurrent use, and enhanced renal toxicity of ACE-inhibitors. Renal function should be checked before starting these medications, and for alogliptin, liver function studies should be checked prior to initiation.[3]

Discussion:
Efficacy in hemoglobin A1C reduction are similar across the four approved medications when used as monotherapy for glycemic control, ranging from 0.5% to 1.5% reduction.[4,5,6,7,8,9] In particular, sitagliptin showed a greater reduction (-1.52%) in A1C in patient's whose initial value was greater than 9%.[5] A 2008 Cochrane review of all DPP-4 inhibitors found no improved metabolic control over other hypoglycemic medications, no increased weight gain, and no statistically significant increase of all cause infections.[10] Theoretical benefits of DPP-4 inhibitors over other oral hypoglycemic medications include a lower incidence of hypoglycemia, associated weight loss, and pancreatic beta-cell protection.[11,12]. Multiple meta-analyses have attempted to compare DPP-4 inhibitors in

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combination with other hypoglycemic agents. Craddy et al. compared DPP-4 inhibitors in combination with metformin, sulfonylureas, metformin plus sulfonylureas, pioglitazone and insulin. They concluded that there were equivalent effects across the class in efficacy and safety and that the only therapy comparison reaching statistically significant difference was alogliptin plus metformin where patients achieved A1C <7% more frequently than those with saxagliptin plus metformin.[13] In 2017, Lin et al. compared DPP-4 inhibitors to placebo and to SGLT2 inhibitors in combination with insulin and found no difference in A1C reduction between SGLT2 inhibitors and DDP-4 inhibitors (0.18% vs. 0.16%). Both were better than placebo but with covariate analysis, SGLT2 inhibitors reduced A1c significantly more in combination with insulin with hypoglycemic events being equal.[14] A 2016 Cochrane review looking at insulin monotherapy versus oral agents plus insulin found that insulin plus DPP-4 inhibitors showed a mean decrease in A1c of 0.4% (95% CI: -0.5 to -0.4; $p<0.01$) and less weight gain (-0.7kg to 1.3kg) versus insulin alone (0.6kg-1.1kg).[15]

With respect to prevention of secondary cardiovascular (CV) outcomes, several large studies looking at major adverse cardiovascular events (MACE) have been conducted. The SAVOR-TIMI 53 trial was an RCT with 16,492 patients using saxagliptin with A1C ranging from 6.5-12% and median duration of exposure of 2.1 years. The primary CV endpoint as a composite of CV death, non-fatal MI, and non-fatal stroke occurred in 7.3% of saxagliptin patients and 7.2% with placebo. Ultimately saxagliptin proved non-inferior ($p<0.001$) to placebo in the primary outcome (but not superior) however there were more hospitalizations for heart failure (3.5% vs. 2.8%, $p=0.007$) with the intervention.[16] In the TECOS trial over 14,000 patients were randomized to placebo or sitagliptin for the same composite primary endpoint as the SAVOR-TIMI trial. There were no differences in the primary or secondary composite outcomes, CV death from any cause was unchanged, and while the incidence of pancreatitis was higher it was not statistically significant.[17] Meta-analysis of CV outcomes with DPP-4 inhibitors included the aforementioned large RCTs. Monami et al.'s meta-analysis of DPP-4 inhibitors vs. placebo or any oral or injectable hypoglycemic therapy (including insulin) showed an overall reduction in MACE (OR 0.71, $p<0.001$, 63 trials). Other statistically significant differences favoring DDP-4 inhibitors included reduced MI (OR 0.64, 95% CI: 0.44-0.94; 41 trials) and all-cause mortality (OR 0.60, 95% CI: 0.41-0.88; 30 trials).[18]

Concerns about significant adverse events with DPP-4 inhibitors have been studied. Toh et al. conducted a retrospective cohort study comparing rates of hospitalization for heart failure (HF) in patients using saxagliptin and sitagliptin. Overall risk of HF was not increased with DDP-4 inhibitors and when patients were stratified according to prior CVD or high HF risk, no increases in hazard ratios were found.[19] A 2014 meta-analysis showed that overall risk of HF hospitalization was higher for DPP-4 inhibitors, however, if the analysis excluded the SAVOR-TIMI trial, there was no increase in risk.[20] Sitagliptin, saxagliptin and linagliptin have been studied for their impact on renal impairment. In a trial of sitagliptin, serum creatinine increased 1.6% vs. 7.7% in the sitagliptin vs. placebo/glipizide groups, respectively. Similarly, in the saxagliptin study, 13.3% of sitagliptin patients (vs. 23.8% of placebo patients) increased from moderate to severe renal impairment.[21] Lastly, several meta-analyses failed to show any increased rate in pancreatitis with DPP-4 inhibitor treatment.[22]

Current guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recommend tailored therapy for second line treatment (after metformin) and include DPP-4 inhibitors in these therapies. The American College of Endocrinology and the American Association of Clinical Endocrinologists recommend DPP-4 inhibitors as second or third line or as a monotherapy in metformin-intolerant patients with an A1c <7.5%.

Conclusions:
DPP-4 inhibitors are safe and effective at lowering blood glucose in patients with T2DM both alone and in combination with other oral and injectable hypoglycemic agents. The risk of hypoglycemia is not increased with DPP-4 inhibitors. DPP-4 inhibitors may reduce CVD risk in long-term studies. Studies have shown increased risk of HF with DPP-4 inhibitors, however the data is skewed by a single large trial, thus clinically, saxagliptin should likely not be used in patients with high risk of HF. DPP-4 inhibitors do not increase risk of pancreatitis. DPP-4 inhibitors are safe in patients with all stages of renal failure.

For questions about 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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Indian Health Service
National Pharmacy and Therapeutics Committee
PCSK9 Inhibitors
NPTC Formulary Brief
August Meeting 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 cause (along with other factors such as fatty substances, cellular waste products, calcium, and fibrin) 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 PSCK9 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.

For questions about 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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