Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *SGLT-2 Inhibitors (Update)*

-November 2019-

Background:

In August 2017, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the sodium-glucose cotransporter-2 inhibitor (SGLT2i) medications for the treatment of diabetes. At that time the committee did not add a SGLT2i due to lack of long-term data, initial safety concerns regarding amputations, and concerns about generalizability of the benefits of the medications to all populations. This class of medications was re-evaluated at the November 2019 meeting due to updated guidelines from the American Academy of American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) as well as new data regarding renal and cardiovascular outcomes of these medications. The NPTC voted to **add empagliflozin to the IHS National Core Formulary**.

Discussion:

It is estimated that more than 30 million Americans currently live with diabetes and that only 25% of those cases have been diagnosed[1]. American Indian/Alaska Native (AI/AN) adults are 2.4 times as likely as white adults to be diagnosed with diabetes with an estimated 30% of the AI/AN population having pre-diabetes[2]. Death rates due to diabetes for AI/AN are 1.6 times higher than the general U.S. population and the incidence of kidney failure due to diabetes is 1.9 times higher[2]. The Strong Heart Study (a large ongoing cohort study of cardiovascular disease in AI/AN) suggested that risk for cardiovascular (CV) disease in AI/AN adults is three to eight times higher than those without diabetes[3]. With the CV and renal complications of diabetes disproportionately affecting the IHS patient population, medications that improve outcomes in CV disease and renal disease could substantially improve the health of our patients.

Currently, four large randomized, placebo-controlled trials (RCT) have been published studying three of the FDA approved SGLT2i medications. The EMPA-REG trial was designed and powered to demonstrate CV outcomes with empagliflozin. This study was the first and only to demonstrate reduction in all-cause mortality as well as significant reduction in CV death, MI, cerebrovascular accident (CVA) and death from any CV cause which resulted in numbers needed to treat (NNT) between 38 and 71 for these outcomes[4]. A post-hoc analysis of EMPA-REG data on renal endpoints reported decreases in worsening nephropathy and a renal composite outcome (doubling of serum creatinine, initiation of renal-replacement therapy and death from renal disease) as well as lower rates of acute renal failure and acute kidney injury in patients receiving empagliflozin[5]. The CANVAS study evaluated canagliflozin and CV outcomes and ultimately reported significant decreases in CV death, MI and CVA (the primary endpoint) in those receiving canagliflozin but did not show significant improvements in all-cause mortality or death from CV disease[6]. The DECLARE-TIMI 58 trial was a RCT of dapagliflozin and its effect on renal and CV outcomes which, while adequately powered and with similar design as the aforementioned studies, did not result in significant impact on the primary outcomes[7]. The June 2019 CREDENCE trial, a RCT of canagliflozin and placebo looking specifically at renal outcomes, suggested that canagliflozin had better renal outcomes than empagliflozin. The trial was stopped early after interim analyses showed a 30% lower relative risk of the primary outcome (end-stage kidney disease, composite) in the canagliflozin group, a difference of 18 events per 1000 patient years less (NNT=23)[8]. While the CREDENCE trial was designed to measure CV outcomes, due to early cessation of the study and differences in population cohorts, it was difficult to draw conclusions about its impact on CV disease and death.

While no head-to-head trials of canagliflozin and empagliflozin exist, a 2019 meta-analysis which included the CANVAS and EMPA-REG studies deemed empagliflozin superior in all CV outcomes[9]. A small, single center retrospective trial in India (N=148) showed similar efficacy in A1C lowering and improvement in estimated glomerular filtration rates (eGFR) among all three SGLT2i, with no significant differences in adverse events[10]. Another meta-analysis also published in 2019 pooled the outcomes from the EMPA-REG, CANVAS, DECLARE, and CREDENCE trials and reported a 35% reduction in risk of end stage renal disease and a 42% risk reduction in composite renal scores without significant difference across all studies[11].

Lastly, in consideration of the safety profile of these medications, canagliflozin does have a boxed warning for increased risk of lower limb amputations, with an increased incidence of about 2.9

amputations per 1,000 patient years as reported in the CANVAS (5.9 vs. 2.8 events per 1000 patient years) and CANVAS-R trials (7.5 vs. 4.2 events per 1000 patient years)[8,12].

New guidelines from the AACE/ACE referenced above echoed the findings of these four trials and while guidelines published in 2017 did not indicate a preference for second-line, noninsulin therapy for diabetic control, the 2019 guidelines specifically state "certain GLP-1 RAs and SGLT2is have shown CVD and CKD benefit – preferred in patients with these complications. Include one of these medications if CHD present"[13]. These recommendations also appear in the American College of Cardiology 2018 guidelines which mention use of SGLT2i, especially in patients with congestive heart failure[14].

=General Considerations for Use=

- All SGLT2i are contraindicated in patients with an eGFR of <30 milliliters/minute
- Expected A1C reduction is 0.5-0.8% when used as monotherapy or add-on therapy
- Improvement in CV outcomes in the EMPA-REG study were seen only in patients with type 2 diabetes AND established cardiovascular disease
- Boxed warning for increased limb amputations with canagliflozin only
- Increased rates of genital mycotic infections, urinary tract infections and necrotizing fasciitis of the groin have all been reported however these increases were not significant in larger trials[15]
- For CVD, SGLT2i should NOT replace appropriate medical therapy for other CV disease risk factors such as cholesterol management

Conclusions:

Cardiovascular disease and renal disease in type 2 diabetes disproportionately affects AI/AN populations. SGLT2i medications likely have a drug class effect of improving both cardiovascular and renal outcomes in diabetic patients. Empagliflozin has the strongest data for improvement in all cause-mortality, cardiovascular mortality, and renal outcomes. As such, empagliflozin was selected to the IHS National Core Formulary as the preferred SGLT2i in the treatment of cardiovascular and renal disease in patients with type 2 diabetes.

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.

References:

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