Background:
The IHS National Pharmacy & Therapeutics Committee (NPTC) reviewed the class of sodium-glucose co-transporter 2 inhibitors (SGLT2i) at the February 2017 meeting. Prior to this, the NPTC performed an initial review of SGLT2i in February 2014 although the evaluation included only canagliflozin and dapagliflozin and neither were added to the National Core Formulary (NCF). As a result of the clinical and pharmacoeconomic evaluation in February 2017, the NPTC did not add any SGLT2i agents to the NCF.

Discussion:
The SGLT2i class of medications currently include canagliflozin, dapagliflozin and empagliflozin. These medications produce anti-glycemic effects through reduction of blood glucose via increased urinary glucose excretion\(^1\). All SGLT2i are approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes mellitus (T2DM). Unlike other anti-diabetic agents, SGLT2i ability to lower glucose levels is independent of insulin and their use is rarely associated with hypoglycemia.

Randomized, controlled trials report that SGLT2i reduce A1c values on average from 0.5-0.7% (versus placebo) although A1c reductions have been noted from 0.4-1.1% depending on baseline levels. Direct comparisons of SGLT2i to active comparator treatments (metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, insulin) yielded modest, non-significant A1c reductions for SGLT2i of 0.06-0.13%\(^2\)\(^-\)\(^5\).

SGLT2i offer benefit beyond that of glycemic control, most notably with reductions in body weight and blood pressure. Several meta-analyses report weight loss (versus placebo) ranging from 1 to 3 kilograms which appears to be both sustained and independent of dose\(^5\)\(^-\)\(^7\). Compared with placebo, use of SGLT2i demonstrated a significant loss of body weight (-2.99 kg, 95% CI: -3.64 to -2.34) following 1 and 2 years of use\(^5\). Additionally, no significant differences in weight loss exist between the SGLT2s\(^7\). Reductions in blood pressure range from -2 to -6 mmHG for systolic blood pressure and -1 to -3 mmHG for diastolic blood pressure\(^6\)\(^,\)\(^7\). The exact mechanism for SGLT2i-associated lowering of body weight and blood pressure remains unknown but is theorized to relate to their osmotic, diuretic effects. SGLT2i are primarily indicated in T2DM patients with estimated Glomerular Filtration Rate (eGFR) of >60 ml/min. Canagliflozin and empagliflozin may be used in patients with eGFR <60 ml/min but >45 ml/min, however lower doses of canagliflozin are recommended. The SGLT2i are contraindicated in both patients with eGFR <45 ml/min and patients with type 1 diabetes mellitus. Prior to SGLT2i initiation, kidney function should be assessed at baseline and periodically during SGLT2i treatment.

The most common adverse events reported with SGLT2i include genital and urinary tract infections (UTI) and hypotension. All SGLT2i are associated with significantly higher rates of mycotic genital infections\(^6\) (Odds Ratio: 4-6 versus placebo) while only dapagliflozin was found to have significantly more UTIs and genital mycotic infections than placebo\(^9\). A safety concern of serious UTIs requiring hospitalization has issued by the FDA. Due to the diuresis with SGLT2i, hypotension is a concern in older patients or patients receiving concomitant antihypertensive agents. Additional safety concerns have been published by both the FDA and Health Canada regarding the association between SGLTs and acute kidney injury\(^10\) (canagliflozin, dapagliflozin), diabetic ketoacidosis\(^11\)\(^,\)\(^12\) (SGLT2s), bone fractures\(^13\)\(^,\)\(^14\) (canagliflozin) and amputations\(^15\) (canagliflozin).

In December 2016, empagliflozin received an additional FDA approval for risk reduction of cardiovascular mortality in adults with T2DM and established cardiovascular disease. This indication resulted from the EMPA-REG trial\(^16\), an international, post-marketing cardiovascular safety study (n=7020). The trial compared empagliflozin to placebo in patients with T2DM and established cardiovascular disease (secondary prevention) who were receiving standard care.

The primary outcome in the EMPA-REG trial was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI) and nonfatal stroke. It was found to be statistically significantly reduced
by 14% (Hazard ratio (HR): 0.86, CI 95%: 0.74-0.99, p=0.04 for superiority) with a number needed to treat of 63, over 3.1 years of treatment with empagliflozin. No differences in the primary outcome were noted between the two doses of empagliflozin (10mg, 25mg). Lower rates of cardiovascular death (HR 0.62, CI:0.49-0.77, p<0.001) and death from any cause (HR 0.68, CI: 0.57-0.82, p<0.001) contributed significantly towards the primary outcome results as neither MI and stroke rates differed from placebo.

Although EMPA-REG is the only SGLT2i cardiovascular trial to date to report statistically significant reductions in cardiovascular mortality, at least one analysis suggests this may be a class effect. A 2016 meta-analysis of 71 studies reported statistically significant reduction in all-cause mortality, cardiovascular mortality and MI, but not stroke. After removing the cardiovascular outcomes trials (i.e., EMPA-REG), no differences were noted among SGLT2i17. The remaining cardiovascular safety studies, CANVAS (canagliflozin) and DECLARE (dapagliflozin), should be completed in 2017 and 2019 respectively and will provide clarity on a potential class effect and the role of SGLT2i in primary and secondary prevention.

The 2017 American Association of Clinical Endocrinologists / American College of Endocrinology recommend SGLT2i as potential second- or third-line therapeutic options, after metformin. The 2017 American Diabetes Association guidelines also recommend SGLT2i as second-line agents, alongside 5 other anti-diabetic classes, when dual therapy is required. Metformin remains the preferred initial agent. A section was added with the recommendation to consider empagliflozin or liraglutide (when added to standard care) in T2DM patients with established cardiovascular disease to reduce mortality risk.

Findings:
The SGLT2i represent a novel, therapeutic addition to the current armamentarium of medications for the management of T2DM. In general, contemporary diabetic guidelines recommend SGLT2i as adjunctive therapy with metformin when necessary. In addition to their modest glucose-lowering effect, SGLT2i offer additional, favorable effects including weight loss and blood pressure reductions, and at least one SGLT2i has demonstrated a reduction in cardiovascular risk to date. The NPTC will collectively evaluate multiple anti-diabetic pharmacotherapy classes at the August 2017 NPTC meeting.

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:
1. Desantis A. Sodium-glucose co-transporter inhibitors for the treatment of type 2 diabetes mellitus. In: UpToDate, Nathan DM (Ed), UpToDate, Waltham, MA (Accessed on February 24, 2017).
15. FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate. Published May 18, 2016. Available here.