A.29	SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT-2) INHIBITORS – Type 2 Diabetes
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The prevalence of diabetes has nearly doubled worldwide since 1980. It is currently one of the leading causes of death and it consumes significant portion of the global healthcare expenditure. Metformin and life style modifications are considered first line therapy but in most cases additional pharmacological interventions are eventually needed.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Metforim and glicazide are included in the EML as hypoglycaemic agents. Additional options are needed for many patients with diabetes in order to achieve appropriate glycaemic control and avoid potential sequelae.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable *Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).* Network meta-analysis did not show benefits of SLGT-2 inhibitors over metformin as monotherapy. The addition of SLGT-2 to an initial regimen lowered all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure (high certainty). They also decreased HbA1C compared to the standard therapy and may help with weight reduction. Results were more significant in patients with established cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease. Studies developed to evaluate the impact of SLGT-2 inhibitors inpatients with renal disease showed similar results: Reduction in risk of hospitalization for heart failure, cardiovascular death, and adverse kidney outcomes (worsening kidney failure, ESKD, or renal death)

	Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Yes. It included patient with different risk levels (It included patients with CAD/ macro vascular disease, atrial fibrillation, heart failure, CKD, albuminuria, etc.). Studies were developed in multiple countries around the world.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: A well conducted systematic review did not find evidence that an SGLT-2 inhibitors added to background therapy increased severe adverse events and it did not increase the hypoglycaemia events to a greater extent than placebo. The most common adverse effect of SGLT-2 inhibitors is genital infections. Most of the time, such infections are mild and can be managed with topical antifungal medications and self-care practices. Discontinuation from the clinical trial due to these infections was uncommon. Fournier's gangrene is a serious but infrequent adverse event associated with SGLT-2 inhibitor use (more common in men than in women and diabetes is a predisposing factor). There is conflicting evidence about increased risk of UTIs. Since SLGT-2 inhibitors generate glycosuria they can lead to osmotic diuresis. It usually leads to increased urinary frequency and increased thirst. Rarely it is associated with orthostatic hypotension secondary to volume depletion. Risk factors for volume depletion are age >75 years, eGFR <60 mL/min/1.73m2 and use of loop diuretics. SLGT-2 inhibitors are also associated with euglycaemic diabetic ketoacidosis. Additionally they seem to be associated with increased risk of DKA. Recent evidence does not show association between SLGT-2 inhibitors and bone fractures o limb amputation
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: DKA is a concerning potential complication. Patients should be aware of symptoms and to get care immediately. Additionally euglycemis DKA is particularly concerning since it generates milder symptomatology and lower values of glucose that can delay diagnosis. Certain risk factors require special considerations: • Patients >75 years old especially those using loop diuretics due to the risk of volume depletion • They should be temporarily discontinued in patients presenting severe UTI, acute illness associated with fasting and dehydrations • Permanently discontinued in patients with history of recurrent UTI. May need to be discontinued in patients with recurrent genital infections

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable. SLGT-2 inhibitors have shown to be beneficial as second line drugs in the treatment of type 2 diabetes based on a well conducted systematic review of RCTs. Benefits is more significant in patient with higher risk of cardiovascular and/or rneal events. Adverse events are in general, manageable.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	High quality of evidence since it comes from well-conducted systematic reviews of RCTs (including studies with large sample sizes) at low-moderate risk of bias.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Physicians and patients should be aware of the potential side effects and appropriate treatment
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	For LMIC these medications may result expensive, compared to other options but their benefits seem to justify the additional cost. Limited evidence suggests they are cost-benefit compared to other treatment options. Price in the United States is around $500 for 30 tablet of 100mg[1]
Any additional comments	

Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Include as send line therapy in patients with type 2 diabetes that have not achieve appropriate control with metformin. High quality of evidence show there are beneficial in this population with a reasonable safety profile. Additionally, limited evidence suggests that SLGT-2 inhibitors are a cost-effective option as second line treatment of type 2 diabetes.
References (if required)	1. GoodRx.com