A.29 (item number)	Sodium-Glucose Co-transporter-2 (SGLT-2) inhibitors – Type 2 Diabetes (application title)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Diabetes affects a significant number of people globally and continue to rise especially in LMIC. Cardiovascular diseases or chronic kidney disease are common comorbid of type 2 diabetes.
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.	SGLT-2 inhibitors are use as an addition to the 1st line therapy (metformin; already included in the EML) and life-style modification especially for patients with CVD and CKD, compelling needs to minimize hypoglycemia or in need to promote weight loss (ADA-EASD Consensus 2018)
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).* A review to inform the development of WHO 2018 guidelines on type 2 diabetes, reported that SGLT-2 inhibitors, performed similarly with other hypoglycemic agents (sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, TZDs and basal insulins, bolus insulins, biphasic insulins, meglitinides, alpha-glucosidase inhibitors, and GLP-1 Ras) added to metformin in lowering A1c compared to placebo.

	There was lower risk of severe hypoglycaemia with SGLT-2 inhibitors (OR 0.09, 95% CI: 0.02, 0.44) compared to sulfonylurea and SGLT-2 inhibitors were associated with weight loss. A review to inform the development of the 2020 Australian Evidence-Based Clinical Guidelines reported that compared to placebo, DPP-4 inhibitor, sulfonylurea or GLP-1 RA as add-on therapy, SGLT-2 inhibitors lowered odds of all-cause mortality, odds of hospitalisation for heart failure, as well as decreased kidney failure, decreased HbA1c, and incurred lower odds of serious adverse events compare to placebo or standard treatment. The certainty of evidence are from moderate to high. Palmer et al (2021), reported that addition of SGLT-2 inhibitors to existing diabetes treatment lowered all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure (high certainty evidence). SGLT-2 inhibitors reduced mortality and admission to hospital for heart failure more than GLP-1 RA, and GLP-1 RA reduced non-fatal stroke more than SGLT-2 inhibitors (which appeared no have no effect). The absolute benefits varied substantially across patients from low to very high risk of cardiovascular and renal outcomes. The benefit consistently increased in accordance to the increase of risk category of the patients especially in term of all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, kidney failure and hospital admission for heart failure. The numerous RCTs and systematic reviews have consistently demonstrated with high certainty the benefits of SGLT-2 inhibitors on important CVD and renal outcomes in people with T2D, especially those at higher risk. *Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?* no data on SGLT-2 inhibitor use in pregnant and breast-feeding women with T2. most of the studies were conducted in high-income countries cost-effectiveness studies were mostly from high-income countries which stated cost-effective. Only 2 studies conducted in middle income countries (Mexico and China) which stated cost-effective.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The most common adverse effect is genital infections. The serious but rare adverse event is Fournier's gangrene. Evidence on the severe urinary tract infections (UTIs) associated with SGLT-2 inhibitors have been conflicting. Small risk intravascular volume depletion, such as hypotension, syncope and dehydration. An increased risk of Diabetic Keto Acidosis (DKA) is also reported, but the event rate is low (<1 to 3 per 1000 patients)

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable benefit especially for patients with risk of or established CVD and CKD.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of evidence ranges from moderate to high certainty
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: Should be used with caution in people with T2D in the following situations: • frail elderly people especially those using loop diuretics due to the risk of volume depletion • severe UTI – use should be temporarily discontinued • history of recurrent UTIs – may need to be permanently discontinued • genital infections – usually respond to genital hygiene but may need to be discontinued if problem is recurrent • conditions of fasting and dehydration

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: Already gained regulatory approval in US, EMA, Japan, Australia and Canada
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: In the WHO 2018 Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus, the recommendation was for patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea, if insulin is unsuitable, a DPP-4 inhibitor, SGLT-2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence). However newer and better evidence on the benefit of SGLT-2 inhibitor has since been established, which resulted in the recommendation of its use in the most recent guideline by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) and the Australian Evidence-Based Clinical Guidelines for Diabetes 2020.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	The benefit especially for patients with risk of CVD and CKD outweigh the risk of adverse events. Cost effectiveness in high income countries have been proven, yet in LMIC it is still depend on the possibility of getting a far lower price for the drugs.

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.	Based on the evidence on its benefits, it is recommended to include the SGLT-2 inhibitor in the EML.
References (if required)	World Health Organization. Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus [Internet]. 2018 [cited 2021 Feb 14]. Available from: https://apps.who.int/iris/bitstream/handle/10665/272433/9789241550284-eng.pdf Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018 Dec; 41(12): 2669-2701. Living Evidence for Diabetes Consortium. Australian Evidence-Based Clinical Guidelines for Diabetes 2020. Australian Evidence-Based Clinical Guidelines for Diabetes. Melbourne, Australia2020. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2021;372:m4573