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# Evidence summary on dapagliflozin for type 2 diabetes mellitus

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| Service Line | Evidence Summary |
| Publication Date | Version 1: 07 March 2023 |
| Approval of the Secretary of Health | Pending |
| Summary Length | 25 Pages |
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# Context of the Review

The Health Technology Assessment (HTA) Council reviewed the clinical and cost-effectiveness evidence and recommendations of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines considering the inclusion of Dapagliflozin in the complementary list of the WHO Essential Medicines List (EML) in 2021. Dapagliflozin is indicated for the treatment of adult patients with Type 2 Diabetes Mellitus (T2DM) to improve glycemic control in combination with metformin when metformin alone or with existing therapy [i.e., metformin, sulfonylurea, metformin and a sulfonylurea, sitagliptin (alone or with metformin) insulin (alone or with metformin)], along with diet and exercise, do not provide adequate glycemic control. It is considered as a therapeutic alternative of empagliflozin for the same indication as stated in the 2021 WHO EML.

The initial assessment included dapagliflozin 5 and 10 mg single-dose tablets (SDT), which was based on the original application to the former Formulary Executive Council (FEC). Since only dapagliflozin 10 mg SDT is available in the Philippines, the assessment focused on this form.

The HTA Council reviewed the clinical evidence and recommendations of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines considering the inclusion of Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors in the Core List of the WHO Essential Medicines List (EML) in 2021. The treatment guidelines of the American Diabetes Association for January 2022 and International Society for Nephrology CPG (KDIGO 2020) were used as the basis for managing T2DM. In addition, the HTA Council considered available local and/or international Clinical Practice Guidelines (CPG). In this assessment, the HTAC also considered the expiring patent of dapagliflozin 10 mg SDT in May 2023 and therefore included in the costing analysis a scenario where the price of dapagliflozin 10 mg SDT is the anticipated lower price for generic counterpart (i.e., 40% of the set maximum wholesale price of the government).

# Policy Question

Should dapagliflozin be included in the Philippine National Formulary for the treatment of Type 2 Diabetes Mellitus as second-line therapy after metformin?

# Research Questions

Clinical Assessment

- Among adult T2DM patients including subpopulations with chronic kidney disease (CKD) and/or atherosclerotic cardiovascular disease (ASCVD) inadequately controlled on MET monotherapy, what is the efficacy of MET+DAP (metformin plus dapagliflozin) compared to other dual therapies which are listed in the PNF namely, MET+GLL/GLC (Metformin plus gliclazide or gliclazide MR) in terms of glycemic control and health-related quality of life?
- Among adult T2DM patients including subpopulations with CKD and/or ASCVD inadequately controlled on MET monotherapy, what is the safety of MET+DAP (metformin plus dapagliflozin) compared to other dual therapies which are listed in the PNF namely, MET+GLL/GLC (Metformin plus gliclazide or gliclazide MR) in terms of adverse events including MACE and serious adverse events, all-cause mortality, fracture events, and kidney and liver function?

Economic Impact Assessment

- What are the associated medical costs per patient using dapagliflozin compared to gliclazide for patients with T2DM including subpopulations with chronic kidney disease (CKD) and/or atherosclerotic cardiovascular disease (ASCVD) inadequately controlled on MET monotherapy?
- What is the total medication cost for the expected number of patients using dapagliflozin compared to gliclazide for patients with T2DM including subpopulations with chronic kidney disease (CKD) and/or atherosclerotic cardiovascular disease (ASCVD) inadequately controlled on MET monotherapy?

- What is the 5-year budget impact of using dapagliflozin compared to gliclazide among patients with T2DM, including subpopulations with chronic kidney disease (CKD) and/or atherosclerotic cardiovascular disease (ASCVD) inadequately controlled on MET monotherapy?
- Is dapagliflozin cost-effective compared to gliclazide among patients with T2DM including subpopulations with chronic kidney disease (CKD) and/or atherosclerotic cardiovascular disease (ASCVD) inadequately controlled on MET monotherapy?

# Key Findings

| Criteria | Judgment |
|---|---|
| **Clinical Efficacy, Effectiveness, and Safety** | Based on studies cited by the WHO including SRMAs with moderate to high quality, SGLT2 inhibitors were shown to have comparable (non-fatal stroke, 3-item MACE) to better efficacy in terms of lowering the odds of all-cause mortality, HbA1c level, cardiovascular outcomes (hospitalization due to heart failure, 4-item MACE), and renal events (kidney failure), as well as improving body weight as compared to both placebo and other antidiabetic medications.<br><br>Studies from the WHO showed a mixed but acceptable safety profile for SGLT2 inhibitors. Based on four studies, SGLT2 inhibitors resulted in higher odds for genital infection related to glycosuria, and increased risk of diabetic ketoacidosis and Fournier's gangrene compared to placebo or other antidiabetic drugs. On the other hand, based on two studies, there is lower risk for bone fracture compared to placebo or other antidiabetic drugs. |
| **Affordability and Viability** | The estimated individual cost of treatment per year using DAP regimens for T2DM patients ranged from ₱18,162.40 to ₱27,864.10 for patients who will not experience genitourinary infections. An additional ₱120.40 is estimated to be incurred if the patient experiences mild genitourinary infection which is the most common adverse event associated with the use of DAP. Overall, DAP FDC regimens incurred a higher cost compared to DAP SDT regimens.<br><br>On the other hand, the estimated individual cost of treatment per year using GLC regimens ranged from ₱18,366.80 to ₱20,761.20 with GLC 30 mg MR incurring the highest cost. The cost of managing mild hypoglycemia which is the most common AE associated with GLC is minimal and paid out of pocket.<br><br>Overall, all current price offers of DAP interventions incurred a higher individual cost per patient compared to the PNF-listed GLC.<br><br>However, it can be noted that DAP can incur a lower cost than GLC upon patent expiration in May 2023 since generic counterparts in their anticipated market entry are estimated to have a lower government price offer than the current maximum wholesale price of DAP. The HTAC notes that as of January 2023 generic counterparts of DAP have already been granted with Certificate of Product Registrations (CPR), however, the expected reduction of price is still not certain.<br><br>In addition, the estimated total cost of DAP regimen for all expected users in 2024 ranged from ₱30.32 B to ₱46.46 B which is relatively higher that the total cost of GLC regimens which ranged from ₱30.55 B to ₱34.54B. |
| | The estimated total budget impact of the DAP regimen from 2023 to 2028 (range: ₱200.02 B to ₱306.48 B) is generally higher than the GLC regimen (range: ₱201.54 B to ₱227.81 B). DAP can incur a lower cost than GLC upon patent expiration in 2023 since generic counterparts in their anticipated market entry in 2023 are estimated to have a lower government price offer than the current maximum wholesale price of DAP. The HTAC notes that as of January 2023, generic counterparts of DAP have already been granted with Certificate of Product Registrations (CPR), however, the expected reduction of price is still not certain.<br><br>Furthermore, DAP is expected to avert the costs of managing heart failure (HF) and chronic kidney disease (CKD) complications due to T2DM based on the |

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|---|---|
| | aforementioned clinical judgment as compared to background diabetes therapy, and other antidiabetic medications.<br><br>The difference between the averted cost of hospitalization due to heart failure of DAP vs GLC cannot be quantified due to unavailability of data of trials that directly compared DAP and GLC on patients with T2DM inadequately controlled on MET monotherapy. However, based on our computation, the potential maximum averted cost of hospitalization due to heart failure as a result of adding DAP to background therapy vs background therapy alone is at ₱290.2 M. Meanwhile, the potential maximum averted cost of dialysis as a result of adding DAP to background therapy vs background therapy alone is at ₱31.09 B. This is based on a study where 80% of the patients were on MET as part of background therapy, but which included other glucose lowering therapies. It is likely that the computed maximum averted cost of hospitalization due to heart failure and cost of dialysis is underestimated. |
| **Cost-effectiveness** | The research question cannot be answered directly due to unavailability of evidence.While the WHO review has shown that the administration of Dapagliflozin as add-on to metformin is cost-effective, none of these studies were conducted in LMICs, and therefore may not be applicable to the Philippines. A local study by Tumanan et al. was found but was deemed not applicable for adoption since their intervention and comparator regimen did not match the research questions of this assessment and the discounting rate used in the study is lower than the PH reference case. |

# Recommendation:

HTA Council **recommends the inclusion of DAP 10 mg single-dose film-coated tablet** in the PNF on the basis of the following:

- Compared to placebo and sulfonylureas, DAP shows acceptable safety profile and comparable efficacy as second-line therapy for type 2 diabetes mellitus patients. SGLT2 inhibitors including DAP have beneficial effects on renal function (lessen kidney failure outcomes), cardiovascular outcomes (lessen hospitalization due to heart failure outcomes, 4-item MACE), obesity, and lower odds of all-cause mortality.
- The current price of the patented DAP is higher than the PNF-listed drug GLC. The SC notes however, that DAP may incur a lower cost than GLC upon the expected entry of the generic counterparts in May 2023 since they are estimated to have a government price offer lower than the current maximum wholesale price of DAP. The expected price reduction is still not certain.
- Cost estimation showing the potential of DAP to avert the cost of dialysis and hospitalization due to heart failure are favorable.

# Annex I: Summary of clinical efficacy and safety evidence and recommendations of the WHO and CPGs

## Supporting Clinical Practice Guidelines

Based on consultation with an endocrinologist in July 2022, the January 2022 American Diabetes Association [ADA] Guidelines was the current guideline being adopted for practice in the Philippines. The 2022 American Diabetes Association [ADA] Recommendations on Pharmacologic Therapy for Adults with Type 2 Diabetes Mellitus are as follows:

- Other medications (glucagon-like peptide [GLP] 1 receptor agonists, ***sodium–glucose cotransporter [SGLT] 2 inhibitors)***, with or without metformin based on glycemic needs, are appropriate *initial therapy* for individuals with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease [ASCVD], heart failure [HF], and/or chronic kidney disease [CKD] **(***Level of evidence:* **A)**
- Among individuals with type 2 diabetes who have established *atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure*, a ***SGLT2-inhibitor*** and/or GLP1-receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of patient-specific factors **(***Level of evidence:* **A)**.

***ADA evidence-grading system***

*Level of evidence:* ***A***

- *Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including*
  - *Evidence from a well-conducted multicenter trial*
  - *Evidence from a meta-analysis that incorporated quality ratings in the analysis*
- *Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford*
- *Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including*
  - *Evidence from a well-conducted trial at one or more institutions*
  - *Evidence from a meta-analysis that incorporated quality ratings in the analysis*

*The following guideline was also cited in the WHO review on sodium-glucose cotransporter-2 (SGLT2) inhibitors, specific for CKD.*

International Society for Nephrology, 2020

Level 1 (strong) recommendation for treating patients with type 2 diabetes mellitus who have an estimated glomerular filtration rate greater than 30 ml/min per 1.73m$^2$ with an SGLT2 inhibitor.

*Note:*

The HTA Council has been apprised of the update in the ADA Guideline last October 2022 and International Society of Nephrology last November 2022 which also recommends using dapagliflozin as first-line therapy for Atherosclerotic Cardiovascular Disease (ASCVD) ,Heart Failure (HF), and Chronic Kidney Disease (CKD) patients in addition to being a second-line therapy. However, in consideration of the 2021 WHO EML recommendations adopted in this review and the immediate provision of access to dapagliflozin for T2DM patients inadequately controlled on metformin, the Council decided to retain the research questions of this review.

## Clinical Evidence from the WHO Essential Medicines List (EML)

**WHO EML approved indication:** Dapagliflozin [DAP] as add-on treatment for adults with Type 2 Diabetes Mellitus [T2DM] patients who have or at high risk of cardiovascular disease and/or diabetic nephropathy

*Clinical research question:*

- Among adult T2DM patients including subpopulations with **chronic kidney disease (CKD) and/or atherosclerotic cardiovascular disease (ASCVD)** inadequately controlled on MET monotherapy, what is the efficacy of MET+DAP (*metformin plus dapagliflozin)* compared to other dual therapies which are listed in the PNF namely, MET+GLL/GLC *(Metformin plus gliclazide or gliclazide MR)* in terms of glycemic control and health-related quality of life?
- Among adult T2DM patients including subpopulations with **CKD and/or ASCVD** inadequately controlled on MET monotherapy, what is the safety of MET+DAP (*metformin plus dapagliflozin)* compared to other dual therapies which are listed in the PNF namely, MET+GLL/GLC *(Metformin plus*

*gliclazide or gliclazide MR)* in terms of adverse events including MACE and serious adverse events, all-cause mortality, fracture events, and kidney and liver function?

**WHO recommendation:**
The WHO added sodium-glucose cotransporter-2 (SGLT2) inhibitors to the core list of EML in 2021 with a squared box listing including empagliflozin as a representative drug and dapagliflozin and canagliflozin as therapeutic alternatives. Specifically, these drugs were recommended as add-on treatments to metformin for adults with type 2 diabetes mellitus who have or are at high risk of cardiovascular disease and/or diabetic neuropathy. The following were the clinical evidence considered for their positive recommendation:

## General findings of the review

- **Efficacy:** Since SGLT2 inhibitors were last reviewed by the WHO Expert Committee in 2017, updated evidence review in 2021 has confirmed the positive effect of SGLT2 inhibitors as an add-on to metformin compared with placebo on all-cause mortality, cardiovascular outcomes (cardiovascular mortality, non-fatal myocardial infarction and hospital admission for unstable angina), renal outcomes (kidney failure, end-stage renal disease and renal death), body weight and HbA1c.
- **Safety:** The WHO Expert Committee considered that SGLT2 inhibitors are associated with some relevant adverse events such as increased risk for urogenital infections, Fournier gangrene, osmotic diuresis and euglycemic diabetic ketoacidosis. However, overall, the benefit-to-risk ratio favors SGLT2 inhibitors, particularly in patients with cardiovascular and kidney disease.

## Evidence considered by the WHO

### A. Systematic Reviews

*Diabetes Society Australia, 2020 [Systematic Review and Network Meta-analysis of 730 trials (an Evidence-based Clinical Guidelines)]*

*Interventions: SGLT2 inhibitors (dapagliflozin, empagliflozin or canagliflozin), DPP-4 inhibitors, GLP-1 RAs or sulfonylureas as add-on to therapy to any existing medication*
*Comparator: Placebo or other interventions in the SR*

While the WHO cited the conclusions made from this guideline, the detailed results including point estimates from its systematic review are not yet publicly available. The study noted that the full systematic review is currently available only to their review panel in confidence and other Australian government institutions (i.e. NHMRC , DOH) for review purposes only. Furthermore, the study used the ReCode calculator in categorizing cardiovascular risks in patients.

*Efficacy outcomes:*

- **All-cause mortality**: Based on high or moderate certainty evidence, SGLT2 inhibitors lowered the odds of all-cause mortality compared with placebo, DPP-4 inhibitors, GLP-1 RAs or sulfonylureas as add-on therapy in patients with very low cardiovascular risks.
- **Hemoglobin A1c**: Based on high certainty evidence, SGLT2 inhibitor therapy decreased HbA1c compared with standard therapy.
- **Hospitalization for heart failure**: Based on high or moderate certainty evidence, SGLT2 inhibitors lowered the odds of hospitalization for heart failure compared with placebo, DPP-4 inhibitors, GLP-1 RAs or sulfonylureas when added to background treatment in patients with very low cardiovascular risks.
- **Major adverse cardiovascular event (MACE)**:
    - ***Three-item MACE*** (composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke): Based on moderate certainty evidence, there was no evidence that SGLT2 inhibitors lowered the odds of a MACE event compared with placebo when added to background therapy.
    - ***Four-item MACE*** (three-item plus hospitalization for unstable angina): Based on high to moderate certainty evidence, SGLT2 inhibitors probably lowered the odds of a MACE event compared with placebo or GLP-1 RAs added to background therapy in patients with very low cardiovascular risks.
- **Kidney failure**: Based on high or moderate certainty evidence, SGLT2 inhibitors decreased kidney failure compared with placebo when added to background therapy in patients with very low cardiovascular risks.

*Safety outcomes:*

- **Severe hypoglycemia:** Based on high or moderate certainty evidence, there was no statistically significant difference between SGLT2 inhibitor added to background therapy as compared to placebo in terms of severe hypoglycaemia.
- **Serious adverse events**: Based on high to moderate certainty evidence, the odds of serious adverse events were lower with SGLT2 inhibitors than standard care in patients with very low cardiovascular risks. Based on high certainty evidence, there was no evidence that other therapies added to background therapy had different odds of serious adverse events.

*Palmer et al., 2021 [Systematic Review and Network Meta-analysis of 764 trials]*

*Interventions: SGLT2 inhibitors or Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) added to other diabetes treatment*
*Comparator:* ***Placebo****, standard of care, or other glucose-lowering treatments*

The study categorized cardiovascular risks in patients as follows: "*very low*" if with no or less than three cardiovascular risk factors; "*low*" if with three or more cardiovascular risk factors; "*moderate*" if with cardiovascular disease; "*high*" if with chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); and "*very high*" if with cardiovascular disease and chronic kidney disease.

*Efficacy outcomes:*

- **All-cause mortality**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- SGLT2 inhibitors lowered all-cause mortality compared with placebo (OR 0.85, 95% CI, 0.79 to 0.92).

| Fewer events/1000 in 5 years | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 3 (moderate) | 10 (high) | 18 (high) | 26 (high) | 40 (high) |

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs*

- SGLT-2 inhibitors and GLP-1 receptor agonists had similar effects on all cause mortality (OR 0.95, 95%CI 0.86 to 1.06).

| Fewer events/1000 in 5 years | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 1 (moderate) | 4 (high) | 6 (high) | 9 (high) | 13 (N/A) |

- **Cardiovascular mortality**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- SGLT-2 inhibitors significantly lowered cardiovascular mortality compared with placebo (OR 0.84, 95%CI 0.76 to 0.92).

| Fewer events/1000 in 5 years | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 2 (moderate) | 7 (high) | 12 (high) | 16 (high) | 24 (high) |

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs added to other diabetes treatment*

- SGLT-2 inhibitors and GLP-1 receptor agonists had no statistically significant different effects on cardiovascular mortality (OR 0.96, 95%CI 0.84 to 1.09).

| Fewer events/1000 in 5 years *[figures from actual study]* | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 0 (moderate) | 2 (high) | 3 (high) | 4 (high) | 5 (N/A) |

- **Non-fatal myocardial infarction**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- SGLT-2 inhibitors significantly lowered the odds of non-fatal myocardial infarction compared with placebo (OR 0.87, 95%CI 0.79 to 0.97).

| Fewer events/1000 in 5 years | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 4 (moderate) | 7 (high) | 13 (high) | 14 (high) | 21 (high) |

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs added to other diabetes treatment*

- SGLT-2 inhibitors and GLP-1 receptor agonists had no statistically significant different effects on non-fatal myocardial infarction (OR 0.95, 95% CI: 0.84 to 1.08).

| Fewer events/1000 in 5 years *[figures from actual study]* | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 1 (moderate) | 3 (high) | 5 (high) | 5 (high) | 7 (N/A) |

- **<u>Non-fatal stroke</u>**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- SGLT-2 inhibitors had little or no effect on non-fatal stroke (OR 1.01, 95%CI 0.89 to 1.14).

| Fewer events/1000 in 5 years *[figures from actual study]* | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 0 (moderate) | 1 (high) | 1 (high) | 1 (high) | 2 (high) |

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs added to other diabetes treatment*

- SGLT-2 inhibitors had significantly higher odds of non-fatal stroke than GLP-1 receptor agonists (OR 1.20, 95%CI 1.03 to 1.41)

| Fewer events/1000 in 5 years *[figures from actual study]* | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 5 (moderate) | 9 (high) | 16 (high) | 18 (high) | 27 (N/A) |

- **<u>Kidney failure</u>**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- SGLT-2 inhibitors significantly reduced incidence of kidney failure (OR 0.71, 95%CI 0.57 to 0.89).

| Fewer events/1000 in 5 years | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 1 (moderate) | 3 (high) | 6 (high) | 25 (high) | 38 (high) |

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs*

- SGLT-2 inhibitors and GLP-1 receptor agonists had no statistically significant different effects on kidney failure (OR 0.91, 95%CI 0.69 to 1.20).

| Fewer events/1000 in 5 years *[figures from actual study]* | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 0 (low) | 1 (moderate) | 1 (moderate) | 6 (moderate) | 10 (N/A) |

- **<u>Hospital admission for heart failure</u>**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- SGLT-2 inhibitors significantly reduced admission for heart failure (OR 0.70, 95% CI 0.63 to 0.77).

| Fewer events/1000 in 5 years |
|---|

| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
|---|---|---|---|---|---|
| No. of events (certainty) | 2 (moderate) | 9 (high) | 23 (high) | 29 (high) | 58 (high) |

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs added to other diabetes treatment*

- SGLT-2 inhibitors significantly reduced hospitalization for heart failure compared with GLP-1 receptor agonists (OR 0.74, 95%CI 0.65 to 0.85).

| Fewer events/1000 in 5 years | | | | | |
|---|---|---|---|---|---|
| Type of patient | Very low risk | Low risk | Moderate risk | High risk | Very high risk |
| No. of events (certainty) | 1 (moderate) | 7 (high) | 18 (high) | 24 (high) | 48 (N/A) |

- **Body weight**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- Based on low certainty evidence, SGLT2 inhibitors result in significantly lower body weight over six months (mean difference (MD) -1.92 kg, 95%CI −2.23 to −1.62) compared to placebo.

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs added to other diabetes treatment*

- Based on moderate certainty evidence, SGLT-2 inhibitors appeared to significantly lower body weight to a greater extent than GLP-1 receptor agonists (MD −0.47 kg, 95%CI −0.85 to −0.09).

- **Glycated hemoglobin A1c**

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: Placebo*

- Based on low certainty evidence, SGLT-2 inhibitors (MD −0.60%, 95%CI −0.67 to −0.54) resulted in significantly lower glycated hemoglobin A1c levels compared to placebo.

*Interventions: SGLT2 inhibitors added to other diabetes treatment*
*Comparator: GLP-1 RAs added to other diabetes treatment*

- Based on high certainty of evidence, GLP-1 receptor agonists significantly reduced glycated hemoglobin A1c levels to a greater extent than SGLT-2 inhibitors (MD −0.28%, 95%CI −0.37 to −0.19).

*Safety outcomes*

- **Adverse events**: Based on high certainty evidence, the odds of genital infection related to glycosuria was higher in SGLT2 inhibitors as compared with placebo. This was concluded from 143 (119 to 170) more genital infections per 1000 patients treated for 5 years (OR 3.50 (95% CI: 3.01,4.07)). The increased risk of genital mycotic infections with SGLT2 inhibitors in both men and women is consistent across all clinical trials.

*KDIGO, 2020 [Systematic Review and Network Meta-analysis (Clinical Practice Guidelines)]*

*Interventions: SGLT2 inhibitors added to metformin*
*Comparator: Placebo*
*Quality assessment: High overall quality of evidence (no quality of evidence indicated per outcome)*

*Efficacy outcomes*

- *Cardiovascular outcomes:*
  - **MACE:** For trial participants with an eGFR of 30 to <60 ml/min per 1.73 $m^2$, the hazard of having MACE outcomes is 18% lower among those who were in the SGLT2i arm as compared with those in the placebo arm (HR: 0.82; 95% CI: 0.70–0.95) .
  - **Risk of hospitalization for heart failure**: For trial participants with an eGFR of 30 to <60 ml/min per 1.73 $m^2$, SGLT2 inhibitors significantly reduced the risk of hospitalization for heart failure by 40% (HR: 0.60; 95% CI: 0.47–0.77) as compared to the placebo arm.
- *Heart failure outcomes*
  - **Composite outcomes for heart failure for hospitalization or death**: Overall, trial participants on SGLT2 inhibitors had significantly lower risk for this outcome as compared to placebo.
    - 28% lower in patients with an eGFR ≥60 ml/min per 1.73 $m^2$ [HR: 0.72 (95% CI: 0.62–0.82)]
    - 23% lower in patients with an eGFR <60 ml/min per 1.73 $m^2$ [HR: 0.77 (95% CI: 0.68–0.88)]

- *Kidney outcomes:*
    - **Composite kidney outcome**: Participants with an eGFR of 30 to <60 ml/min per 1.73 $m^2$, SGLT2i significantly reduced the hazard of adverse kidney outcomes by 33%(worsening kidney failure, ESKD, or renal death; HR: 0.67; 95% CI: 0.51–0.89) as compared to placebo.
    - **Risk of dialysis, transplant, or renal death**: SGLT2i significantly reduced the risk of dialysis, kidney transplant, or renal death by 33% (RR: 0.67; 95% CI: 0.52–0.86) as compared to placebo.

*Neuen et al., 2019 [Systematic Analysis and Meta-analysis of 4 RCTs]*

*Interventions: SGLT2 inhibitors added to background therapy*
*Comparator: **Placebo***
*Quality assessment: Low risk of bias for all indicators*
*Efficacy Outcomes*

- **Dialysis, Transplantation, or death due to kidney disease:** Overall, SGLT2 inhibitors significantly reduced the risk of dialysis, transplantation, or death due to kidney disease (RR 0.67, 95% CI 0.52–0.86, p=0.0019)
    - End-stage kidney disease: SGLT2 inhibitors significantly reduced the risk of end-stage kidney disease (RR 0.65, 053–0.81, p<0·0001) with consistent benefits across studies
    - Acute kidney injury: SGLT2 inhibitors significantly reduced the risk of acute kidney injury (RR 0.75, 0.66–0.85, p<0·0001), with consistent benefits across studies
    - Adverse kidney outcomes: SGLT2 inhibitors were associated with a reduced risk of adverse kidney outcomes – worsening kidney failure, end-stage kidney disease or renal death in patients with GFR of <60 mL/min:
        - 24 % lower in patients with GFR 30 to <60 mL/min per 1.73$m^2$ [HR 0.76, 95% CI 0.51 to 0.89 *(WHO Selection 2021)]*
        - 30% lower in patients with GFR 30 to 45 mL/min per 1.73$m^2$ [HR 0.70, 95% CI 0.54 to 0.91 *(From the actual study)]*

*Liu et al., 2015 [Systematic review and meta-analysis of 39 RCTs]*

*Interventions: SGLT2 inhibitors with or without other antihyperglycemic agents*
*Comparator: Placebo or other antidiabetic drugs*
*Safety Outcomes*

- **Adverse events**: Based on high quality evidence, SGLT2 inhibitors resulted in a significantly increased risk of diabetic ketoacidosis compared with placebo or other antidiabetic drugs (Peto OR 2.13, 95% CI 1.38 to 3.27), with an absolute rate of 3 events per 1000 patients over 5 years.

*Li et al, 2019 [Systematic Review and Meta-analysis]*

*Interventions: SGLT2 inhibitors with background therapy*
*Comparator: Placebo or other antidiabetic drugs*
*Quality assessment: Most trials showed a low risk of selection, detection and attrition bias, while one had relatively high risk of bias.*

*Safety Outcomes*

- **Adverse events:** SGLT2 treatment was not associated with a higher risk of bone fracture [pooled risk ratio (RR) 1.02, 95% CI, 0.81, 1.28, with low heterogeneity].

## B. Randomized Controlled Trials

*Wiviott et al., 2019 (DECLARE–TIMI 58 trial) [Phase III RCT]*

*Interventions: Dapagliflozin with or without other diabetes medications*
*Comparator: Placebo*
*Efficacy outcomes*

- **Renal composite outcomes *(40% reduction in eGFR to < 60 mL/min per 1.73$m^2$, end-stage kidney disease and cardiovascular or or renal death):*** The hazard of having adverse renal outcomes was 24% lower in the dapagliflozin arm as compared to placebo (HR 0.76, 95% CI 0.67 to 0.87).

*Perkovic et al. 2019 (CREDENCE) [Phase III RCT]*

*Interventions: Canagliflozin in addition to background therapy*
*Comparator: Placebo*
*Efficacy outcomes*

- **Progression of albuminuria:** Canagliflozin was significantly associated with a lower risk of progression of albuminuria (HR 0.73, 95% CI 0.67 to 0.79).
- **Renal composite outcomes:** The hazard of having adverse renal composite outcomes was 40% lower in the canagliflozin arm as compared to placebo (HR 0.60, 95% CI 0.47 to 0.77). These outcomes include 40% reduction in eGFR, need for kidney replacement therapy or death from renal cause.

*Wanner et al., 2018 (EMPA-REG OUTCOME) [Phase III RCT]*

*Interventions: Empagliflozin added to background therapy*
*Comparator: Placebo*
*Efficacy outcomes*

- **Nephropathy**: The hazard of having or worsening nephropathy was 39% lower in the empagliflozin arm as compared to placebo compared with placebo (−12.7% versus 18.8% (HR 0.61, 95% CI 0.53 to 0.70).

*Heerspink et al., 2020 [Phase III RCT]*

*Interventions: Dapagliflozin added to background therapy*
*Comparator: Placebo*
*Efficacy Outcomes*

- **Composite of renal failure, or death from renal or cardiovascular causes**: The hazard of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo.
    - 39% lower in chronic kidney disease patients [HR: 0.61; 95% CI, 0.51 to 0.72; P<0.001]
    - 36% lower in chronic kidney disease patients with type 2 diabetes [HR: 0.64; 95% CI, 0.52 to 0.79]
    - 50% lower in chronic kidney disease patients with no type 2 diabetes [HR: 0.50; 95% CI, 0.35 to 0.72]
- **Composite of renal failure, or death from renal causes (renal-specific outcome):** The risk of composite renal specific outcomes was significantly lower in the dapagliflozin than with the placebo arm **(**HR: 0.56; 95% CI, 0.45 to 0.68; P<0.001).

### C. Observational studies

*Kosiborod et al., 2017 [Observational multi-country cohort study]*

*Interventions: SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) as initial or add-on therapy*
*Comparator: Other glucose-lowering agents (metformin, sulfonylurea, DPP-4 inhibitors, thiazolidinediones, GLP-1 receptor agonist, insulin,acarbose, amylin analog, meglitinides)*
*Quality assessment: Not performed*
*Efficacy Outcomes*

- **All-cause death:** The hazard of all-cause death was 51% lower in the SGLT-2 inhibitors arm as compared to other glucose-lowering agents (HR 0.49; 95% CI, 0.41–0.57; P<0.001)
- **Composite of Hospitalization for Heart Failure (HHF) or Death:** The hazard HHF or death was 46% lower in the SGLT-2 inhibitors arm as compared to other glucose-lowering agents was associated (HR 0.54; 95% CI, 0.48–0.60; P<0.001).

*Heerspink et al., 2020 [Observational cohort study]*

*Interventions: SGLT2 inhibitors added to background therapy*
*Comparator: Other glucose-lowering drugs*
*Efficacy Outcomes*

- **Rate of eGFR decline:** SGLT2 inhibitor initiation was significantly associated with reduced eGFR decline. The difference in slope was at 1.53 mL/min per 1.73 m2 per year, 95% CI 1.34–1·72, p<0.0001
- **Composite kidney outcomes (eGFR decline of 50% or end-stage kidney disease):** The hazard of composite renal specific outcomes was 51% lower in the dapagliflozin than with the placebo arm. **(**HR: 0.49; 95% CI, 0.35 to 0·67; p<0.0001)

*Abrahami et al., 2019 [Population-based cohort analysis]*

*Interventions: SGLT2 inhibitors did not report it mono- or combination therapy*
*Comparator: DPP4 inhibitors*
*Safety Outcomes*

- **Adverse events:** The hazard of bone fractures was 3% lower in the SGLT2i arm compared to DPP-4 inhibitors (HR 0.97, 95% CI 0.79–1.19).

## D. National Regulatory reports

*Bersoff-Matcha, 2019 [Post-marketing review]*

*Interventions: SGLT2 inhibitors with or without other antihyperglycemic agents*
*Comparator: Other antiglycemic agents*
*Quality assessment: Not performed*
*Safety Outcomes*

- **Rare adverse events**: Fournier gangrene is a serious but rare adverse event associated with the use of SGLT2 inhibitors. US Food and Drug Administration identified 55 cases of Fournier gangrene in 6 years of SGLT2 inhibitor use compared with 19 cases over 35 years for all other drugs that lower blood glucose.

*United States Food and Drug Administration (US FDA)*

*Safety Outcomes*

- In May 2015, the US FDA issued a drug safety communication warning that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis.
- The US FDA warning on canagliflozin about the increased risk of amputations was removed in 2020.

# Annex II: Costing Analysis

*Comparative costing analysis and budget impact analysis between DAP and GLC were performed, following the judgment for clinical evidence that DAP is non-inferior to GLC.*

*Inputs to the costing analysis*

The HTA Council compared the government procurement price (i.e. DPRI price) of the PNF-listed drug Gliclazide [GLC] to the government price offered by the patent holder of Dapagliflozin [DAP] and the potential government price offer by its generic counterparts upon their market entry which is 40% lower than Maximum Wholesale Price, MWP). The council notes that as of February 2023, there are four local manufacturers/distributors of generic DAP counterparts already granted with Certificates of Product Registration (CPR) by the Philippine FDA. However, these companies are not yet able to distribute their products due to the existing patent held by the innovator company which is expected to expire by May 2023. The projected price reduction of these generic DAP counterparts are still uncertain, but a 40% price reduction was used for this analysis based on consultation with the DOH Pharmaceutical Division (DOH-PD). Furthermore, the recent addition of two other indications for DAP (i.e. chronic kidney disease, heart failure even without diabetes) is not expected to cause an extension of the innovator patent based on the Cheaper Medicines Act of 2008, 2015 Intellectual Property Code of the Philippines and consultation with the DOH-PD.

Prices for different dosage strengths and dosage forms for both GLC and DAP were also reflected for comparison. Direct medical cost items included the cost of the drug regimen (i.e. both for the intervention/comparator and the add-on metformin) and the cost of adverse event (AE) management for the most common AEs associated with the use of DAP and GLC which are mild urinary tract infection (UTI) and mild hypoglycemia, respectively at a public payer/government perspective for one year. Other direct medical costs such as the cost of HbA1c monitoring and check-ups, were omitted in this analysis since these costs are incurred for both interventions and comparators (hence, will cancel off and will not affect the incremental cost). Direct non-medical costs (e.g. transportation) and indirect costs (i.e. opportunity costs) were also not included in his analysis.

The dosing regimens utilized in the analysis were consulted with Philippine College on Endocrinology, Diabetes, and Metabolism (PCEDM) wherein the maximum daily dose was recommended as assumption for this analysis and all regimens were in addition to metformin [MET] based on treatment guidelines. According to the PCEDM, the duration of dapagliflozin treatment for T2DM usually lasts for a lifetime. For this costing analysis the comparative treatment costs were presented for one year. The total number of users were extrapolated using the T2DM prevalence of the Philippines in the Global Burden of Disease study (2010-2019). A total of 4.752 million Filipinos are estimated to have T2DM in 2023. An adjustment factor of 32.90% metformin failure based on the Weiss et al., 2021 study projecting 1,563,476 Filipinos expected to use second-line oral antidiabetic drugs in 2023. From these, the final costing outputs were the total costs of treatment regimen per patient and for all expected users.

Four different price offers for DAP were compared with three different dosage strengths of GLC. All interventions and comparators were treated as add-on to the unit price of MET from DPRI, 2022. Below are the references for the unit prices of these different forms of DAP and GLC, used in the calculation:

| | **Drug**<br>**Dosage Strength (Dosage Form)** | **Price Reference** | |
|---|---|---|---|
| | | ***for the intervention/Comparator*** | ***for the add-on MET*** |
| INTERVENTION | Dapagliflozin 10mg (SDT) + Metformin 500 mg (SDT) | Innovator Price Offer:<br>MWP (EO 104 s 2020) | DPRI 2022 |

| | | | |
|---|---|---|---|
| | Dapagliflozin 10mg (SDT) + Metformin 500 mg (SDT) | Generic counterpart Projected Price Offer: 40% lesser than the MWP (EO 104 s 2020)* | |
| | (Dapagliflozin 10mg / Metformin 1g) (FDC) + Metformin 500 mg (SDT) | Innovator Price Offer | |
| | Dapagliflozin 5mg / Metformin 1g (FDC) | Innovator Price Offer | |
| | Gliclazide 80mg (SDT) + Metformin 500 mg (SDT) | DPRI 2022 | |
| | Gliclazide 60mg (SDT) + Metformin 500 mg (SDT) | DPRI 2022 | |
| COMPARATOR | Gliclazide 30mg (SDT) + Metformin 500 mg (SDT) | DPRI 2022 | |

Note: SDT = Single dose tablets
FDC = Fixed-dose combination tablets
**The projected price reduction of these generic DAP counterparts are still uncertain, but a 40% price reduction was used for this analysis based on consultation with the DOH-PD.*

*Key findings of the costing analysis*

- The resulting total individual cost of the DAP regimen ranged from ₱18,162.40 to ₱27,864.10 per patient per year for patients who will not experience genitourinary infections. An additional ₱120.40 is estimated to be incurred if the patient experiences mild genitourinary infection which is the most common adverse event associated with the use of DAP. The total cost of the DAP regimen for all expected users per year ranged from ₱30.32 B to ₱46.46 B.
- The total individual cost per patient per year of GLC 80mg SDT, and GLC 60mg and 30mg MR with add-on MET ranged from₱18,366.80 to ₱20,761.20 with GLC 30 mg MR incurring the highest cost. The cost of managing mild hypoglycemia which is the most common AE associated with GLC is minimal and paid out of pocket. Meanwhile the total cost of the GLC regimen for all expected users per year ranged from ₱30.55 B to ₱34.54 B.
- Overall, all DAP interventions incurred a higher cost per patient and all expected users compared to the PNF-listed GLC. However, it can be noted that DAP can incur a lower cost than GLC upon patent expiration in May 2023 since the generic counterparts, in their anticipated market entry, are estimated to have a lower government price offer than the current maximum wholesale price of DAP. The HTAC notes that as of January 2023, the generic counterparts of DAP have already been granted with Certificate of Product Registrations (CPR). However, the expected reduction of price is still not certain. The detailed computation for the costing analysis is indicated in Table 2.1 below, and comparative costs are detailed in Tables 2.2.

Table 2.1. *Regimen cost computations for DAP and GLC*

| | | | Cost of Intervention/Comparator | | | | Cost of Add-on Metformin | | | | Cost of AE management | | | | | TOTAL INDIVIDUAL COST OF DRUG REGIMEN PER YEAR (without AE) | TOTAL INDIVIDUAL COST OF DRUG REGIMEN PER YEAR (with AE) | TOTAL COST FOR ALL EXPECTED USERS OF DRUG REGIMEN PER YEAR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Single/ Combination** | **Drug Dosage Strength** | **Dosage Form *of I/C*** | **Unit cost of medicine (A)** | **Reference** | **No. of dosage units per unit time (B)<br><br>Dosing regimen** | **Total cost of intervention/comparator per patient per year (D) =A*B** | **Unit cost of medicine (A)** | **Reference** | **No. of dosage units per unit time (B)<br><br>Dosing regimen** | **Total cost of MET per patient per year (D) =A*B** | **Drug management for mild complicated genitourinary infection** | **Reference** | **Cost of management for mild hypoglycemia** | **Reference** | **TOTAL COST OF OTHER COSTS** | | | |
| SDT | DAP 10mg + MET 500 mg | FCT | ₱32.40 | AZ Price Offer<br><br>MWP EO 104 s 2020 | 10 mg/day<br><br>1 tab after breakfast | ₱11,826.00 | ₱7.580 | DPRI 2022 (highest generic price) | 2000mg/day<br><br>2 tablets 2x a day after meals | ₱11,066.80 | ₱120.40 | PSMID Guideline for UTI in Adults<br>Ofloxacin: DPRI 2022 price | | | **₱120.40** | **₱22,892.80** | **₱23,013.20** | **₱35.90 B** |
| SDT | DAP 10 mg + MET 500 mg | FCT | ₱19.44 | 40% lesser than the MWP EO 104 s 2020 | 10 mg/day<br><br>1 tab after breakfast | ₱7,095.60 | ₱7.580 | DPRI 2022 (highest generic price) | | ₱11,066.80 | ₱120.40 | PSMID Guideline for UTI in Adults<br>Ofloxacin: DPRI 2022 price | | | **₱120.40** | **₱18,162.40** | **₱18,282.80** | **₱28. 50 B** |
| FDC | (DAP 10mg / MET 1g) + MET 500 mg | FCT | ₱59.36 | AZ Price Offer | 10 mg/day<br><br>1 tab after breakfast | ₱21,666.40 | ₱7.580 | DPRI 2022 (highest generic price) | 1000mg/day from the add-on SDT<br><br>1 tablet 2x a day after meals | ₱5,533.400 | ₱120.40 | PSMID Guideline for UTI in Adults<br>Ofloxacin: DPRI 2022 price | | | **₱120.40** | **₱27,199.80** | **₱27,320.20** | **₱42.63 B** |
| FDC | DAP 5mg / MET 1g | FCT | ₱38.17 | AZ Price Offer | 10 mg/day<br><br>1 tab 2X a day before meals (2 tablets a day) | ₱27,864.10 | *Not applicable (FDC) Metformin 2000mg/day* | | | ₱0.00 | ₱120.40 | PSMID Guideline for UTI in Adults<br>Ofloxacin: DPRI 2022 price | | | **₱120.40** | **₱27,864.10** | **₱27,984.50** | **₱43.67 B** |

| | | | Cost of Intervention/Comparator | | | | Cost of Add-on Metformin | | | | Cost of AE management | | | | | TOTAL INDIVIDUAL COST OF DRUG REGIMEN PER YEAR (without AE) | TOTAL INDIVIDUAL COST OF DRUG REGIMEN PER YEAR (with AE) | TOTAL COST FOR ALL EXPECTED USERS OF DRUG REGIMEN PER YEAR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Single/ Combination** | **Drug Dosage Strength** | **Dosage Form *of I/C*** | **Unit cost of medicine (A)** | **Reference** | **No. of dosage units per unit time (B)<br><br>Dosing regimen** | **Total cost of intervention/comparator per patient per year (D) =A*B** | **Unit cost of medicine (A)** | **Reference** | **No. of dosage units per unit time (B)<br><br>Dosing regimen** | **Total cost of MET per patient per year (D) =A*B** | **Drug management for mild complicated genitourinary infection** | **Reference** | **Cost of management for mild hypoglycemia** | **Reference** | **TOTAL COST OF OTHER COSTS** | | | |
| SDT | GLC 80mg + MET 500 mg | CT | ₱5.00 | DPRI 2022 (highest generic price) | 320mg/day<br><br>2 tabs 2X a day before meals (4 tablets a day) | ₱7,300.00 | ₱7.580 | DPRI 2022 (highest generic price) | 2000mg/day<br><br>2 tablets 2x a day after meals | ₱11,066.80 | | | ₱0.00 | mild hypoglywon't incur cost to the gov't | **₱0.00** | **₱18,366.80** | **₱18,366.80** | **₱28.72 B** |
| SDT | GLC 60 mg + MET 500 mg | MR | ₱11.58 | DPRI 2022 (highest generic price) | 120mg/day<br><br>1 tab 2X a day before meals (2 tablets a day) | ₱8,453.40 | ₱7.580 | DPRI 2022 (highest generic price) | | ₱11,066.80 | | | ₱0.00 | mild hypoglywon't incur cost to the gov't | **₱0.00** | **₱19,520.20** | **₱19,520.20** | **₱30.52 B** |
| SDT | GLC 30mg + MET 500 mg | MR | ₱6.64 | DPRI 2022 (highest generic price) | 120mg/day<br><br>2 tabs 2X a day before meals (4 tablets a day) | ₱9,694.40 | ₱7.580 | DPRI 2022 (highest generic price) | | ₱11,066.80 | | | ₱0.00 | mild hypoglywon't incur cost to the gov't | **₱0.00** | **₱20,761.20** | **₱20,761.20** | **₱32.46 B** |
| | Placebo | | | | | | ₱7.580 | DPRI 2022 (highest generic price) | | ₱11,066.80 | | | | | **₱0.00** | **₱11,066.80** | **₱11,066.80** | **₱17.30 B** |

Table 2.2. *General Findings on the comparative cost analysis of DAP vs. GLC*

| | DAP 10mg + MET 500 mg SDT [*40% lesser than the MWP*] Generics Estimated Price | GLC 80mg + MET 500 mg | GLC 60mg + MET 500 mg | GLC 30mg + MET 500 mg | DAP 10mg + MET 500 mg SDT [*MWP EO 104 s 2020* (max)] Innovator Price offer | (DAP 10mg / MET 1 g)+ MET 500 mg FDC + SDT Innovator Price offer | DAP 5mg / MET 1 g FDC Innovator Price offer |
|---|---|---|---|---|---|---|---|
| *Individual cost w/o AE* | ₱18,162.40 | ₱18,366.80 | ₱19,520.20 | ₱20,761.20 | ₱22,892.80 | ₱27,199.80 | ₱27,864.10 |
| *Individual cost w/ AE* | ₱18,282.80 | ₱18,366.80 | ₱19,520.20 | ₱20,761.20 | ₱23,013.20 | ₱27,320.20 | ₱27,984.50 |
| **Total Cost for 2024 users** | **₱30.32 B** | **₱30.55 B** | **₱32.47 B** | **₱34.54 B** | **₱38.19 B** | **₱45.36 B** | **₱46.46 B** |
| | **LOWEST COST** | | | | | | **HIGHEST COST** |

# Annex III: Budget Impact Analysis

The budget impact analysis performed covered a 6-year horizon from 2023 to 2028. The estimated number of 2022 T2DM patients was projected using the prevalence rate of T2DM patients in the Philippines from the Global Burden of Disease study data from 2010 to 2019. For succeeding years (i.e. 2023, 2024), the number of new patients were estimated by projecting the incidence of T2DM in the Philippines from the Global Burden of Disease study data from 2010 to 2019. A 32.9% metformin failure rate based on the study of by Weiss et al, 2021 was also factored in per year to estimate the number of users of second-line oral antidiabetic drugs. All other costing assumptions used in the costing analysis in Annex II were also utilized in this analysis. The detailed computation for the budget impact analysis is indicated in Table 3.1 below

The total budget impact of DAP treatment for all expected users from 2023 to 2028 ranged from ₱200.02B to ₱251.93B. DAP treatment incurred a higher budget impact compared to GLC which ranged from ₱201.54 B to ₱227.81 B. Similar to the trend in the costing analysis above, DAP incurred a higher cost than GLC regimen in terms of budget impact incremental costs. The incremental costs are detailed in Table 3.2.

Upon consultation with PhilHealth on their current budget for funding of oral antidiabetics, it was noted that only specific case rates for DM related hospitalization are being reimbursed. Furthermore,the expansion of the Comprehensive Outpatient Benefit Package (COBP) of PhilHealth is also currently being evaluated which can allocate budget for outpatient medications.

Table 3.1 *Budget impact analysis computations for DAP and GLC (in Billion Pesos)*

| YEAR | Total Number of Users | DAP | | | | GLC | | |
|---|---|---|---|---|---|---|---|---|
| | | DAP 10mg + MET 500 mg *Innovator Price** + DPRI* | DAP 10mg + MET 500 mg *Projected Generic* + DPRI* | (DAP 10mg / MET 1g) + MET 500 mg *AZ Price + DPRI* | DAP 5mg / MET 1g *AZ Price* | Gliclazide 80mg + MET 500 mg | Gliclazide 60mg + MET 500 mg | Gliclazide 30mg + MET 500 mg |
| 2023 | 1,563,476 | ₱35.90 B | ₱28.50 B | ₱42.63 B | ₱43.67 B | ₱28.72 B | ₱30.52 B | ₱32.46 B |
| 2024 | 1,663,555 | ₱38.19 B | ₱30.32 B | ₱45.36 B | ₱46.46 B | ₱30.55 B | ₱32.47 B | ₱34.54 B |
| 2025 | 1,768,185 | ₱40.60 B | ₱32.23 B | ₱48.21 B | ₱49.39 B | ₱32.48 B | ₱34.52 B | ₱36.71 B |
| 2026 | 1,877,367 | ₱43.10 B | ₱34.22 B | ₱51.19 B | ₱52.44 B | ₱34.48 B | ₱36.65 B | ₱38.98 B |
| 2027 | 1,991,100 | ₱45.71 B | ₱36.30 B | ₱54.29 B | ₱55.61 B | ₱36.57 B | ₱38.87 B | ₱41.34 B |
| 2028 | 2,109,384 | ₱48.43 B | ₱38.45 B | ₱57.51 B | ₱58.92 B | ₱38.74 B | ₱41.18 B | ₱43.79 B |
| **TOTAL** | **10,973,067** | **₱251.93 B** | **₱200.02 B** | **₱299.19 B** | **₱306.48 B** | **₱201.54 B** | **₱214.20 B** | **₱227.81 B** |

Table 3.2 *Total incremental cost of DAP vs. GLC interventions for all expected users in 2023-2028*

| | | COMPARATOR | | |
|---|---|---|---|---|
| **INTERVENTION** | **Drug / Dosage Strength** | **GLC 80mg + MET 500 mg** | **GLC 60mg + MET 500 mg** | **GLC 30mg + MET 500 mg** |
| **Drug Dosage Strength** | **Total Estimated Budget Impact from 2023-2028** | **₱201.54 B** | **₱214.20 B** | **₱227.81 B** |
| | | **Incremental Costs (Cost of DAP - Cost of Comparator)** | | |
| **DAP 10mg + MET 500 mg *Projected Generic* + DPRI*** | **₱200.02 B** | -₱1.52 B | -₱14.17 B | -₱27.79 B |
| **DAP 10mg + MET 500 mg *Innovator Price** + DPRI*** | **₱251.93 B** | ₱50.39 B | ₱37.73 B | ₱24.12 B |
| **(DAP 10mg / MET 1g) + MET 500 mg *Innovator Price**+ DPRI*** | **₱299.19 B** | ₱97.65 B | ₱85.00 B | ₱71.38 B |
| **DAP 5mg / MET 1G *Innovator Price**** | **₱306.48 B** | ₱104.94 B | ₱92.28 B | ₱78.67 B |

# Annex IV: Projected Averted Costs From Dialysis And Heart Failure Treatment

The HTAC noted from evidence presented in Annex IV that the cost-effectiveness review by the WHO in HICs and the local cost utility analysis concluded that dapagliflozin is cost-effective mainly due to cost savings incurred from averted renal and cardiovascular diseases. Therefore, the HTAC decided to examine the cost savings as a result of averting the cost of dialysis and heart failure treatment that is associated with the use of DAP.

The HTA Council intended to compare the averted costs from dialysis and hospitalization due to heart failure between DAP and GLC, however studies which directly compared DAP and GLC regimens in terms of these outcomes were unavailable. There is a study (Wiviott et al., 2019 ) which looked at DAP in addition to background diabetes therapy versus background diabetes therapy alone (80% of the patients were using metformin, 43% were using sulfonylureas) ; hence, the analysis on averted costs that was calculated (which was based on this study) represents the maximum averted cost of HF and dialysis .

## Estimated Number of T2DM Patients Requiring Dialysis and Hospitalizations due to Heart Failure

For this analysis, the proportion of patients that will require dialysis was derived from the DECLARE-TIMI-58, 2019 randomized controlled trial (RCT) for DAP in addition to background diabetes therapy and background diabetes therapy alone and the ADVANCE RCT for GLC. The prevalence of T2DM patients in 2017 was retrieved from the Global Burden of Disease Study (2019) reduced by a metformin [MET] failure adjustment factor of 32.9% from Weiss et al., 2021. Table 6.1 below details the computation of the number of patients expected to be on dialysis for the year 2023. For the succeeding years (e.g. 2024-2028), we used the similar population inputs with the conducted budget impact analysis detailed in Annex III.

Table 4.1. *Estimated number of T2DM patients requiring dialysis and hospitalizations due to heart failure in 2023*

| | Heart Failure | Dialysis |
|---|---|---|
| **Reference studies** | Wiviott et al., 2019 (DECLARE TIMI-58 trial) | |
| **Median follow-up period** | 4.2 years | |
| **Outcome of interest** | Hospitalization for HF | Composite of end-stage renal disease (ESRD), renal death, and a 40% decrease in estimated glomerular filtration rate (GFR) |
| **Transition Probability [A]** | *2.50%* | *1.48%* |
| **Prevalence of T2DM patient with MET failure in 2018 [B]** | 1,563,476 | 1,563,476 |
| **Estimated T2DM patients needing treatment by 2023 [C=A*B]** | **39,087** | **23,140** |

## Estimated Cost Savings From Dialysis

The PhilHealth case rate for all types of dialysis (i.e. hemodialysis, peritoneal dialysis, etc.) as of October 2022 was used to valuate the cost of dialysis per session which is at ₱ 2,600.00. Based on PhilHealth Circular 2022-0017, the maximum number of sessions per year 144 was assumed to be claimed per patient. Hence, the total cost to the government was estimated to be at ₱ 374,400.00 per patient per year. As detailed in Table 6.2, DAP as an add-on to background diabetes therapy is estimated to incur about ₱31.09 B in savings to the government due to dialysis cases averted as compared to the background diabetes therapy alone in the next five years. .

Table 4.2. Total cost to the government after DAP and background diabetes therapy alone among dialysis patients

| YEAR | TOTAL NUMBER OF PATIENTS | DAP + BACKGROUND DIABETES THERAPY ALONE | BACKGROUND DIABETES THERAPY ALONE | AVERTED DIALYSIS CASE COSTS vs. BACKGROUND DIABETES THERAPY ALONE |
|---|---|---|---|---|
| 2024 | 1,663,555 | ₱2.17 B | ₱4.06 B | ₱1.89 B |
| 2025 | 1,768,185 | ₱4.46 B | ₱8.38 B | ₱3.92 B |
| 2026 | 1,877,367 | ₱6.90 B | ₱12.97 B | ₱6.08 B |
| 2027 | 1,991,100 | ₱9.47 B | ₱17.85 B | ₱8.38 B |
| 2028 | 2,109,384 | ₱12.19 B | ₱23.02 B | ₱10.83 B |
| TOTAL | 9,409,591 | ***₱35.19 B*** | ***₱66.28 B*** | ***₱31.09 B*** |

## Estimated Cost Savings From Heart Failure Hospitalization

The PhilHealth case rate for heart failure as of October 2022 was used to valuate the cost of heart failure hospitalization which is at ₱15,700.00 As detailed in Table 6.3, DAP as an add-on to background diabetes therapy is estimated to incur about ₱290. 02 M in savings to the government due to heart failure hospitalizations averted as compared to the background diabetes therapy alone in the next five years.

Table 4.3. *Total cost to the government after DAP and background diabetes therapy alone among patients who require hospitalization due to Heart Failure*

| YEAR | TOTAL NUMBER OF PATIENTS | DAP + BACKGROUND DIABETES THERAPY ALONE | BACKGROUND DIABETES THERAPY ALONE | AVERTED HF HOSPITALIZATION COSTS vs. BACKGROUND DIABETES THERAPY ALONE |
|---|---|---|---|---|
| 2024 | 1,663,555 | ₱ 150 M | ₱200 M | ₱ 51.2 M |
| 2025 | 1,768,185 | ₱160 M | ₱220 M | ₱54.5 M |
| 2026 | 1,877,367 | ₱170 M | ₱230 M | ₱57.9 M |
| 2027 | 1,991,100 | ₱180 M | ₱250 M | ₱61.5 M |
| 2028 | 2,109,384 | ₱200 M | ₱260 M | ₱65.2 M |
| TOTAL | 9,409,591 | **₱870 M** | **₱116 B** | **₱290.2 M** |

# Annex V: Summary of Evidence from Cost Effectiveness Analysis (CEA) Or Cost Utility Analysis (CUA) Studies

## Evidence considered by the WHO

The WHO Expert Committee on the Selection and Use of Essential Medicines concluded that most of the cost-effectiveness (CE) studies they reviewed found SGLT2 inhibitors to be cost-effective as compared to older classes of second-line glucose-lowering medicines, especially for patients at a high risk of developing cardiovascular disease. The WHO adds that beyond its glucose-lowering effects, the beneficial effects of SGLT2 inhibitors on renal function, cardiovascular outcomes and obesity are key drivers of cost-effectiveness.The cost-effectiveness of SGLT2 inhibitors has been studied in recent systematic reviews and a meta-analyses:

Bagepally et al., 2019 *[Systematic review and meta-analysis of 13 CEA studies]*
*Intervention: SGLT2 inhibitors*
*Comparator: Sulfonylureas; DPP4 inhibitors*
*Quality assessment: Risk of bias assessment was done using the economic evaluations bias (ECOBIAS) checklist (no overall conclusion)*

The systematic review and meta-analysis included mostly high-income countries (10/11 countries included) and used meta-regression and fixed-effects models to compare the cost-effectiveness between SGLT2 inhibitors and sulfonylureas or DPP4 inhibitors. Most of the included studies used a lifetime horizon. Discount rate and base cases were not pooled. Using a willing-to-pay threshold (i.e., ≥$37,732.12), the study indicated that SGLT2 inhibitors were cost-effective as compared with sulfonylureas. On the other hand, SGLT2i's were not cost-effective when compared with DPP4is. The pooled incremental net benefits (95% confidence interval) for these corresponding comparisons were $3675.09 ($1656.46-$5693.71; I2 = 85.4%), and $164.95 (−$534.71 to $864.61; $I^2$ = 0%), respectively. Most of the evidence was from high-income countries with few comparative drug groups. Only 1 study from Mexico (Neslusan et al., 2015) represented upper-middle income countries, while no studies were included for lower-middle to lower economies. The study of Neslusan et al.,2015 concluded that Canagliflozin was more cost-effective than Sitagliptin [ICER= 128,883 Mexican Pesos (MXP) per Quality-adjusted life-years (QALY); threshold = 3 times the Gross Domestic Product (GDP) per capita]. However, the study of Bagepally et al., 2019 adjusted the reported ICER value to purchasing power parity (PPP)-adjusted US dollars for the year 2017. This resulted in an ICER value of −5,635.8 US dollars per QALY gained and an incremental net benefit of 2,696.8 QALY gained.

Hong et al., 2019 *[Systematic review of 85 studies]*
*Intervention: Newer antidiabetic medications (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors)*
*Comparator: Insulin, thiazolidinediones, sulfonylureas, other newer antidiabetic medications*
*Quality assessment: Moderate to good quality of evidence according to CHEERS checklist*

The systematic review listed included mostly high-income countries (20/26 countries included) which used the BRAVO model, CORE Diabetes Model, UK Prospective Diabetes Study model, and other validated health economic diabetes models. It compared newer oral anti-diabetic medications (i.e. GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors) with other antidiabetic medications (i.e. insulin, thiazolidinediones, and sulfonylureas). Discount per annum ranged from 3 to 5% while the CE thresholds were not summarized in the SR. The SR concluded that in most of the reviewed studies, newer antidiabetic medications were found to be cost effective, compared with insulin, thiazolidinediones, and sulfonylureas. There were thirteen studies from five upper-middle income countries which included Argentina (1 study), China (7 studies), Mexico (1 study), Thailand (1 study), Brazil (1 study), and Colombia (1 study); however, only three of these studies evaluated SGLT-2 inhibitors as all the rest reviewed other newer oral-antidiabetics (i.e. GLP-1 receptor agonists, DPP-4 inhibitors). First, is the study of Neslusan et al., 2015 in Mexico which concluded that Canagliflozin was more cost-effective than Sitagliptin [ICER= 128,883 MXP per QALY; threshold = 3 times the GDP per capita ]. The other two studies - Gu et al., 2016 and Shao et al., 2017 both conducted in China concluded that Dapagliflozin is more cost-effective than acarbose [ICER= -33,786 Chinese Yuan (CNY) per QALY; threshold = GDP per capita] and dominant over glimepiride, respectively. No studies were included for lower-middle to lower economies.

Yoshida et al., 2020 *[Systematic review of 24 studies]*
*Intervention: SGLT2 inhibitors*
*Comparator: DPP4 inhibitors, sulfonylureas, GLP-1 RA, SGLT2 inhibitors, thiazolidinediones, AGIs, insulin, metformin, standard of care*
*Quality assessment: Good quality according to CHEERS checklist*

The systematic review included mostly high-income countries (9/11 countries included) and used economic models such as the Cardiff diabetes model, IQVIA Core Diabetes Model, and ECHO-T2DM. It examines the relative cost-effectiveness of SGLT2 inhibitors compared to other antidiabetic drugs

or standard of care. There was high heterogeneity in the methodology (i.e. sources of information, modeling of the disease, types of costs, discount rates, perspective, time horizon, baseline characteristics, etc.) and considerable variations in the populations, countries, threshold, and perspectives in the studies included. Most studies had a lifetime horizon and discount per annum ranged from 1.5 to 5% and concluded that SGLT2 inhibitors in mono, dual, or triple therapy were cost-effective relative to other comparators except with GLP-1 RA. There were two studies which suggested that GLP-1 RA was a more favorable treatment option relative to SGLT2 inhibitors. No studies were included for lower-middle to lower economies. Meanwhile, five relevant studies were from upper middle income countries (UMICs) which included four studies from China and one from Mexico. The following were the reported results from these UMICs:

- The study of Neslusan et al., 2015 in Mexico concluded that Canagliflozin is more cost-effective than Sitagliptin [ICER= 128,883 MXP per QALY; willingness-to-pay threshold = 423,600 MXP per QALY (3 times the GDP per capita)].
- The study of Gu et al., 2016 in China concluded that Dapagliflozin is more cost-effective than acarbose [ICER= -33,786 CNY per QALY; willingness-to-pay threshold = 46,629 CNY per QALY (2014 GDP per capita)].
- The study of Shao et al., 2017 in China concluded that Dapagliflozin is more cost-effective than glimepiride [ ICER= -49,065 CNY per QALY; willingness-to-pay threshold = 46,629 CNY per QALY (2014 GDP per capita)], respectively.
- The study of Cai et al., 2019 in China concluded that Dapagliflozin treatment is more cost-effective than metformin alone [ICER= 10,729 CNY per QALY; willingness-to-pay threshold = 50,251 CNY (GDP per capita)].
- The study of Hou et al., 2019 in China concluded that Canagliflozin is more cost-effective as compared to Dapagliflozin [ICER= 129 USD per QALY; willingness-to-pay threshold = 9,117 USD (2017 GDP per capita)].

In 2018, the Medicines Patent Pool published a feasibility study examining the SGLT2 inhibitor market in detail, in terms of patient access to SGLT2 inhibitors (at the time), pricing, the intellectual property landscape, and potential clinical benefits and cost savings if access were expanded by voluntary licensing through the Medicines Patent Pool model. The Medicines Patent Pool estimated that SGLT2 inhibitor prices could decrease substantially when and where competitive generic manufacture is established.

*Medicines Patent Pool, 2018 [Feasibility study]*
*Intervention: SGLT2 inhibitors*
*Comparator: Other newer antidiabetics*

- The availability and affordability of the newer drug classes for type 2 diabetes treatment (SGLT2 inhibitors, GLP-1 agonists, DPP4 inhibitors) is low in LMICs. Most of these are under patent protection in several LMICs, including those with significant manufacturing capacity (India, China, South Africa, Brazil, Thailand), with patents protecting SGLT2 inhibitors expiring between 2023 to 2029. Examples of these LMICs are:
  - ***Pakistan:*** SGLT2 inhibitors are not registered and not available.
  - ***India*****:** While SGLT2 inhibitors are becoming more popular due to their weight loss effect, DPP4 inhibitors entered the market earlier and are thus still more commonly prescribed and are more affordable. A significant amount of Indians pay their medicines out-of-pocket. Originator SGLT2 inhibitors are currently priced at US$19-23 per month on the Indian private market.
  - ***Cambodia*****:** Less than 1% of those that benefit from SGLT2 inhibitors receive them.
  - ***Tanzania*****:** Some SGLT2 inhibitors were available but only in the private sector, at a high price
- This modeling study suggests that MPP-enabled licensing of generic SGLT2 inhibitors could potentially enable 1.1 to 3.3 million people to access treatment. Based on available data, early access can also lead to cardiovascular benefits of these medicines, this uptake could avert 31,000 to 126,000 cases of MACE, conferring 68,000 to 275,000 additional QALYs.
- When generic market entry becomes possible, prices of SGLT2 inhibitors could become more affordable and this may facilitate their inclusion in national reimbursement schemes, at least for patients at high risk cardiovascular events.

While the evidence presented above shows favorable results, most of these studies were conducted in high income countries and some from upper-middle countries. Estimates of cost-effectiveness outside high-income countries remain limited for SGLT2 inhibitors. The WHO added a caveat that low- and middle-income countries are likely to have lower willingness-to-pay thresholds for cost-effectiveness, and SGLT2 inhibitors will have to have significantly lower prices in low- and middle-income countries (LMICs) than the current originator prices in high-income countries in order to be cost-effective. The Expert Committee also recommended for the Medicines Patent Pool to

explore how to facilitate affordable access to SGLT2 inhibitors in LMICs through public health-oriented licenses with the companies holding the patents.

### Local CUA Study

To supplement the WHO review, an additional local cost utility study Mendoza et al., 2021 submitted by the patent holder of dapagliflozin was also considered in the HTAC review. However, the research questions of the study do not match the PICO of this review and the discounting rate used in the study is lower than the PH reference case (7%). Although the local study has a subgroup analysis for T2DM, it was specifically for patients with heart failure with reduced ejection fraction in contrast with the population of interest of this review which is adult T2DM patients including subpopulations with chronic kidney disease (CKD) and/or atherosclerotic cardiovascular disease (ASCVD) inadequately controlled on MET monotherapy. Moreover, the local study compared dapagliflozin only to those using standard therapy for heart failure with their outcomes more focused on the prevention of worsening heart failure or cardiovascular death rather than safety and efficacy outcomes on type 2 diabetes mellitus.

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