Evidence Summary on insulin glargine and detemir for type 1 and type 2 diabetes mellitus

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Context of the Review

The Health Technology Assessment Council (HTAC) 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 long acting insulin analogs (LAIAs) in the Core List of the WHO Essential Medicines List (EML) in 2021.

In addition, the HTAC considered available local and/or international Clinical Practice Guidelines (CPG) and conducted a costing and budget impact analysis to determine the cost to the government for financing these drugs.

Policy Question

Should long-acting insulin analogues - insulin glargine and detemir be included in the Philippine National Formulary for the treatment of type 1 and type 2 diabetes mellitus?

Research Questions

Clinical Assessment

1. Among patients with **Type 1 Diabetes Mellitus (T1DM)**, are **long acting** insulin analogues (i.e., glargine, detemir) effective (HbA1c, postprandial glucose, FBS, survival, quality of life) and safe (hypoglycemia, survival, QoL) compared to **Neutral Protamine Hagedorn (NPH) Insulin**?
2. Among patients with **Type 2 Diabetes Mellitus (T2DM)** on metformin, are **long acting** insulin analogues (i.e., glargine, detemir) in combination with oral anti-hypoglycemic agents (i.e., metformin and gliclazide) effective (HbA1c, postprandial glucose, FBS, survival, quality of life) and safe (hypoglycemia) compared to **NPH Insulin** in combination with oral anti-hypoglycemic agents (i.e. metformin and gliclazide)?

Economic Assessment

1. What are the associated medical costs per patient using **long-acting** insulin analogues (i.e., glargine, detemir) compared to **NPH Insulin** for patients with **T1DM**?
2. What are the associated medical costs per patient using **long-acting** insulin analogues (i.e., glargine, detemir) compared to **NPH Insulin** for patients with **T2DM**?
3. What is the total medication cost for the expected number of patients using **long-acting** insulin analogues (i.e., glargine, detemir) compared to **NPH Insulin** for patients with **T1DM**?
4. What is the total medication cost for the expected number of patients using **long-acting** insulin analogues (i.e., glargine, detemir) compared to **NPH Insulin** for patients with **T2DM**?
5. Are **long acting** insulin analogues (i.e., glargine, detemir) cost-effective compared to **Neutral Protamine Hagedorn (NPH) Insulin** among patients with **Type 1 Diabetes Mellitus (T1DM)**?
6. Are **long acting** insulin analogues (i.e., glargine, detemir) cost-effective compared to

Neutral Protamine Hagedorn (NPH) Insulin among patients with **Type 2 Diabetes Mellitus (T2DM)**?

Key Findings

The HTAC concluded with the following findings based on its decision framework as stipulated in Republic Act 11223 or the *Universal Healthcare Act*:

Criteria	Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Clinical Efficacy, Effectiveness, and Safety	Insulin glargine and insulin detemir both had comparable efficacy in terms of HbA1c reduction and quality of life in type 1 diabetes mellitus patients compared to NPH insulin. Insulin glargine and detemir both had comparable to better safety profiles compared to NPH insulin in T1DM patients. Specifically, both long-acting insulin analogues had a significantly lower risk of severe and nocturnal hypoglycemia. Meanwhile, there were no statistical or clinically significant differences between long-acting insulin analogues and NPH insulin that were observed for other adverse events. However, based on evidence of low certainty, the WHO noted the association of risk of cancer (pancreas, liver, kidney, stomach, respiratory system) with the exposure to insulin, from a systematic review and meta-analysis of 34 studies. In addition, insulin glargine treatment was also associated with a marginally increased risk of breast cancer, based on low certainty of evidence.	Insulin glargine and insulin detemir both had comparable efficacy in terms of HbA1c reduction, reduction of diabetes related complications, and quality of life in type 2 diabetes mellitus patients compared to NPH insulin. Insulin glargine and detemir both had comparable to better safety profiles compared to NPH insulin in T2DM patients. Specifically, both long-acting insulin analogues had a significantly lower risk of general, severe, and nocturnal hypoglycemia. Meanwhile, there were no statistical or clinically significant differences between long-acting insulin analogues and NPH insulin that were observed for other adverse events. However, based on evidence of low certainty, the WHO noted the association of risk of cancer (pancreas, liver, kidney, stomach, respiratory system) with the exposure to insulin, from a systematic review and meta-analysis of 34 studies. In addition, insulin glargine treatment was also associated with a marginally increased risk of breast cancer, based on low certainty of evidence.
Affordability and Viability	The estimated individual cost of treatment (i.e. cost of drug regimen and administration) using LAIAs for T1DM patients who will not experience severe hypoglycemia	The estimated individual cost of treatment (i.e. cost of drug regimen and administration) using LAIAs for T2DM patients who will not experience severe hypoglycemia

	ranges from ₱11,811.40 for insulin glargine biosimilar vial, and up to ₱28,660.10 for insulin glargine biosimilar pen, while the use of NPH insulin will only incur ₱6,093.68 per patient per year. Meanwhile, if T1DM patients are to experience severe hypoglycemia, the cost of treatment is higher due to the additional cost of adverse event management. In these cases, the total costs are expected to increase to ₱15,811.40 for insulin glargine biosimilar vial to ₱22,566.43 for insulin glargine biosimilar pen, and ₱10,093.68 for NPH insulin vial. The estimated total cost of treatment (i.e., cost of drug regimen and administration, adverse event (AE) management) using LAIAs for all expected T1DM patients in 2022 ranges from ₱1.35B for insulin glargine biosimilar vial, and up to ₱3.23 B for Insulin Glargine biosimilar pen, while the use of NPH insulin will only incur ₱ 737.22 M per year. Overall, the estimated total cost of treatment using long-acting insulin analogues is higher than the comparator NPH insulin. Insulin glargine is generally cheaper than insulin detemir. In terms of delivery systems, vials are cheaper than pens for insulin glargine. In terms of manufacturing, biosimilars are cheaper than the innovator for insulin glargine vials but more expensive than the innovator for insulin glargine pen. These comparisons cannot be made for insulin detemir as the only available price offer was for the innovator pen.	ranges from ₱1,562.40 for insulin glargine biosimilar vial, and up to ₱3,731.25 for insulin glargine biosimilar pen, while the use of NPH insulin will only incur ₱733.50 per patient per year. Meanwhile, if T2DM patients are to experience severe hypoglycemia, the cost of treatment is higher due to the additional cost of adverse event (AE) management. In these cases, the total costs are expected to increase to ₱5,562.40 insulin glargine biosimilar vial to ₱7,731.25 for insulin glargine biosimilar pen, and ₱4,733.50 for NPH insulin vial. The estimated total cost of treatment (i.e., cost of drug regimen and administration, AE management) using LAIAs for all expected T2DM patients in 2022 ranges from ₱1.51 B for insulin glargine biosimilar vial, and up to ₱3.45 B for Insulin Glargine biosimilar pen, while the use of NPH insulin will only incur ₱ 772.00 M per year. Overall, the estimated total cost of treatment using long-acting insulin analogues is higher than the comparator NPH insulin. Insulin glargine is generally cheaper than insulin detemir. In terms of delivery systems, vials are cheaper than pens for insulin glargine. In terms of manufacturing, biosimilars are cheaper than the innovator for insulin glargine vials but more expensive than the innovator for insulin glargine pen. These comparisons cannot be made for insulin detemir as the only available price offer was for the innovator pen.

	The estimated budget impact (i.e., cost of drug regimen and administration, AE management) using LAIAs for all expected T1DM patients from 2022 to 2024 ranges from ₱4.17 B for insulin glargine biosimilar vial, and up to ₱10.01 B for Insulin Glargine biosimilar pen, while the use of NPH insulin will only incur ₱ 2.29 B. Overall, the total cost of treatment using long-acting insulin analogues is higher than the comparator NPH insulin. Insulin glargine is generally cheaper than insulin detemir. In terms of delivery systems, vials are cheaper than pens for insulin glargine. In terms of manufacturing, biosimilars are cheaper than the innovator for insulin glargine vials but more expensive than the innovator for insulin glargine pen. These comparisons cannot be made for insulin detemir as the only available price offer was for the innovator pen.	The total cost of treatment (i.e., cost of drug regimen and administration, AE management) using LAIAs for all expected T2DM patients in 2022 to 2024 ranges from ₱1.71 B for insulin glargine biosimilar vial, and up to ₱3.91 B for Insulin Glargine biosimilar pen, while the use of NPH insulin will only incur ₱0.87 B. Overall, the total cost of treatment using long-acting insulin analogues is higher than the comparator NPH insulin. Insulin glargine is generally cheaper than insulin detemir. In terms of delivery systems, vials are cheaper than pens for insulin glargine. In terms of manufacturing, biosimilars are cheaper than the innovator for insulin glargine vials but more expensive than the innovator for insulin glargine pen. These comparisons cannot be made for insulin detemir as the only available price offer was for the innovator pen.
Cost-effectiveness	Based on cost-effectiveness studies included in the WHO review, the administration of long-acting insulin analogues - insulin glargine and insulin detemir are cost-effective. Most studies concluded that the cost of LAIAs were substantially offset by savings from averted hypoglycemia or diabetes-related complications. However, there is a lack of evidence from lower middle income countries.	

Summary of clinical efficacy and safety evidence and recommendations of the WHO and CPGs

WHO approved indication in the EML	Clinical Evidence from WHO EML	Supporting Clinical Practice Guidelines
Type 1 Diabetes Mellitus Type 2 Diabetes Mellitus patients who are at high risk of experiencing hypoglycemia with human insulin	*Clinical research question:* ● Among patients with T1DM, are long-acting insulin analogues (i.e. glargine, detemir) effective (HbA1c, postprandial glucose, FBS, survival, quality of life) and safe (hypoglycemia, survival, QoL) compared to Neutral Protamine Hagedorn (NPH) Insulin? ● Among patients with T2DM on metformin, are long-acting insulin analogues (i.e., glargine, detemir) in combination with oral anti-hypoglycemic agents (i.e., metformin and gliclazide) effective (HbA1c, postprandial glucose, FBS, survival, quality of life) and safe (hypoglycemia) compared to NPH Insulin in combination with oral anti-hypoglycemic agents (i.e., metformin and-gliclazide)? The WHO added long-acting insulin analogues (insulin glargine, insulin detemir, and insulin degludec) to the core list of EML in 2021 with a squared box listing for these three insulin analogues and their respective biosimilars. Specifically, it was recommended for T1DM and T2DM patients who are at high risk of experiencing hypoglycemia with human insulin. The following were the clinical evidence considered for their positive recommendation: Type 1 Diabetes Mellitus (T1DM): General Findings	Based on consultation with an endocrinologist, the 2022 American Diabetes Association [ADA] Guidelines is the current guideline being adopted for practice in the country. 2022 American Diabetes Association [ADA] Recommendations on Pharmacologic Therapy Adults with Type 1 Diabetes Mellitus ● Most individuals with T1DM should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. (*Level of evidence:* A) ● Individuals with T1DM should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. (*Level of evidence:* B) ● Choices of insulin regimen in

	• Efficacy: The WHO Expert Committee noted that the magnitude of the benefit of insulin detemir and glargine over human insulin in terms of reduced glycated hemoglobin (HbA1c) remains modest. • Safety: The evidence consistently showed advantage of long-acting insulin analogues over human insulin in terms of lower incidence of symptomatic and nocturnal hypoglycemia which is clinically relevant, particularly in the subset of T1DM patients who have frequent severe hypoglycaemia (requiring assistance) with human insulin. Specific studies referred by the WHO review *Laranjeira et. al., 2018 [Systematic Review and Meta-Analysis of 11 Systematic Reviews including 28 RCTs]* *Interventions: Long-acting insulin analogues (insulin glargine and detemir)* *Comparator: NPH insulin* *Quality assessment: Six of 11 SRs presented a methodological quality of 8 to 11 out of a maximum of 11 points on the AMSTAR score. No systematic review was excluded because of poor methodological quality.* *Efficacy outcome:* • Hemoglobin A1c (HbA1c): Long-acting insulin analogues led to a significant reduction of HbA1c levels as compared to NPH insulin. (Mean difference (MD): −0.17, 95% CI −0.23 to −0.12) *Safety outcomes:* • General Hypoglycemia: Long-acting insulin analogues led to a statistically significant reduction of this adverse event as compared to NPH insulin. [Pooled Relative risk (RR) 0.95, 95% CI: 0.91-0.99] • Nocturnal Hypoglycemia Episodes: Long-acting insulin analogues led to a significant reduction of this adverse event as compared to NPH insulin. (Pooled RR 0.66, 95% CI 0.57 to 0.76) • Severe Hypoglycemia: There was no significant difference between long-acting insulin analogues and NPH insulin for this outcome. (Pooled RR 0.94, 95% CI 0.71 to 1.24).	people with type 1 diabetes may vary per patient depending on flexibility, risk of hypoglycemia, and cost. The ADA guideline summarizes these preferences in this table: https://diabetesjournals.org/view-large/figure/4400256/dc22S009f1.tif Adults with Type 2 Diabetes Mellitus Based on the ADA treatment algorithm for T2DM in adults, insulin treatment is recommended as a second-line or third-line agent after metformin therapy and comprehensive lifestyle modifications. Treatment will depend on the comorbidities, patient-centered treatment factors, and management needs of the patient. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. (*Level of evidence:* E) • If insulin is used, combination

	Tricco A.C. et. al., 2021 [Systematic Review and Meta-Analysis of 64 RCTs and 1 non-RCT] *Interventions: Long-acting insulin analogues and biosimilars (insulin glargine, detemir, and degludec)* *Comparator: Human insulin* *Quality assessment: unclear/high ROB was given for the majority of included studies* *Efficacy outcomes:* ● Hemoglobin A1c (HbA1c): Long-acting insulin analogues and biosimilars led to reduced HbA1c as compared to human insulin. [MD: −0.14 %points (95% CI −0.22 to −0.06)] ● Fasting Plasma Glucose (FPG): Long-acting insulin analogues and biosimilars led to reduced FPG as compared to human insulin. [MD: −1.03 mmol/L (95% CI −1.33 to −0.73 mmol/L)]; however there might be bias associated with small study effects. ● Weight: Long-acting insulin analogues and biosimilars led to reduced weight as compared to human insulin. [MD −0.7 kg (95% CI −1.08 to −0.32 kg)]. *Safety outcomes:* Major or serious Hypoglycemia episodes: Long-acting insulin analogues and biosimilars led to significantly fewer episodes as compared to human insulin. (OR: 0.63, 95% CI 0.51 to 0.79) yet there might be bias associated with small-study effects. ● Nocturnal Hypoglycemia Episodes: Long-acting insulin analogues and biosimilars led to significantly fewer episodes as compared to human insulin. (OR: 0.74, 95% CI 0.58 to 0.94) ● Others Adverse Events (all-cause hypoglycemia, vascular complications, microvascular complications, macrovascular complications, any adverse events, serious adverse events and drop-outs due to adverse events): No significant differences *Almeida P. et. al., 2018 [Systematic Review or 4 RCTs and 4 cohort studies]* *Interventions: Insulin Glargine* *Comparator: NPH Insulin*	therapy with a glucagon-like peptide 1 receptor agonist (GLP1 RA) is recommended for greater efficacy and durability of treatment effect. (*Level of evidence:* A) ● Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment. (*Level of evidence:* E) ● Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 IU/kg/day, high bedtime-morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. (*Level of evidence:* E)

	Efficacy outcomes: ● Quality Of Life (QoL): Five studies favored insulin glargine over NPH insulin in certain areas, specifically areas of satisfaction with treatment or perception of hyperglycemia. Meanwhile two studies showed no significant difference and one study did not measure QoL outcomes. In terms of quality, the included cohort studies had an overall moderate quality score, while the RCTs had poor methodological quality. *Cherubini V et. al., 2019 [Systematic Review of 2 real-world studies including Cherubini V et. al., 2014]* *Interventions: Long-acting insulin analogues (Insulin glargine and detemir)* *Comparator: NPH Insulin* *Quality assessment:not performed* ● Serious hypoglycemia: Long Acting Insulin Analogues had a significantly lower incidence rate ratio [IRR] of 0.46 (95% CI 0.22 to 0.95) for this adverse event as compared with NPH insulin. *Wagner VM et.al., 2008 [Prospective Cohort]* *Interventions: Long-acting insulin (did not specify type of analogs were included)* *Comparator:NPH/zinc Insulin* *Quality assessment: not performed* ● Hypoglycemia Episodes: Long-acting insulin analogues led to significantly more episodes than NPH insulin. (OR 1.57, 95% CI 1.21 to 2.03). However, the study noted that causality cannot be deduced from the results of their observational study since confounding factors such as previous history of hypoglycemia was not standardized among patients and might have been influenced by patient and doctor preferences for insulin types. ● Severe hypoglycemia: There was no statistically significant difference between long-acting insulin analogues and NPH insulin. (OR 1.42, 95% CI 0.86 to 2.35).	● The ADA guideline on the intensification to insulin therapy is reflected in this treatment algorithm: https://diabetesjournals.org/view-large/figure/4400279/dc22S009f4.tif Children and Adolescents with T1DM *Glycemic Monitoring, Insulin delivery, and Targets* ● Real-time continuous glucose monitoring B or intermittently scanned continuous glucose monitoring E should be offered for diabetes management in youth with diabetes on multiple daily injections or insulin pump therapy who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on patient circumstances, desires, and needs. ● Insulin pump therapy alone should be offered for diabetes management to youth on multiple daily injections with type 1 diabetes who are capable of using the device safely (either by themselves or

	Hemmingsen B et. al., 2021 [Systematic Review of 26 RCTs with a follow-up of at least 24 weeks] *Interventions: Insulin glargine, detemir, and degludec (analyzed individually and not as a class)* *Comparator: NPH Insulin* *Efficacy outcomes:* ● Hemoglobin A1c (HbA1c): Based on moderate quality of evidence, there was no significant difference in HbA1c reduction between insulin detemir and NPH insulin (MD 0.01%, 95% CI −0.1 to 0.1%) or between insulin glargine and NPH insulin (MD 0.02%, 95% −0.1 to 0.1%). *Safety outcomes:* ● Severe Hypoglycemia: Based on moderate quality of evidence, Insulin detemir was associated with a significantly lower risk of severe hypoglycaemia events than NPH insulin (RR 0.69, 95% CI 0.52 to 0.92). Meanwhile, no significant difference was found between insulin glargine and NPH insulin (RR 0.84, 95% CI 0.67 to 1.04). ● Severe Nocturnal Hypoglycemia: Based on moderate quality of evidence, there was no clear difference regarding the risk of severe nocturnal hypoglycemia. *Czech M et. al., 2015 [Systematic Review of 76 Observational Studies]* *Interventions: Long-acting insulin analogues (insulin glargine and detemir)* *Comparator: NPH Insulin, sulfonylureas in monotherapy, insulin pump* ● Annual Probability Of One Or More Severe Hypoglycaemia: Based on medium to good quality of evidence, event per patient for basal-bolus insulin analogues was at 21.4% (95% CI 11.3% to 43.0%) and 33.8% (95% CI 17.9% to 67.5%) for the basal human insulin arm. Type 2 Diabetes Mellitus (T2DM): General Findings	with caregivers). The choice of device should be made based on patient circumstances, desires, and needs. *(Level of Evidence: A)* ● Less stringent A1C goals (such as <7.5% [58 mmol/mol]) may be appropriate for patients who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulins, advanced insulin delivery technology, and/or continuous glucose monitoring; cannot check blood glucose regularly; or have non glycemic factors that increase A1C (e.g., high glycators). (*Level of Evidence:* B) Children and Adolescents with T2DM Based on the ADA treatment algorithm for T2DM in children, insulin treatment is recommended as a second-line or third-line agent after metformin therapy and comprehensive lifestyle modifications. *Pharmacologic treatment* ● Youth with marked

	• Efficacy: The WHO Expert Committee noted that the magnitude of the benefit of insulin detemir and glargine over human insulin in terms of reduced glycated hemoglobin (HbA1c) remains modest. • Safety: The WHO Expert committee noted that the frequency of severe hypoglycemia in T2DM patients is generally lower than in T1DM, thus the differences in the rates of hypoglycaemia and severe hypoglycaemia between long-acting analogues and human insulin may be more limited. However, the Committee noted that people with type 2 diabetes with long-lasting insulin deficiency can develop an insulin-dependent disease similar to type 1 diabetes. In these people, the frequency of hypoglycaemia events with human insulin progressively rises, potentially leading to more pronounced benefits of insulin analogues. Specific studies referred by the WHO review *Semlitsch T et. al., 2020 [Systematic Review and Meta-Analysis of 24 RCTs]* *Interventions: Insulin glargine, detemir, and degludec (analyzed individually and not as a class)* *Comparator: NPH Insulin* *Efficacy outcomes:* • Hba1c levels: Based on low certainty of evidence, there is no statistically significant difference in terms of mean HbA1c compared to NPH insulin [MD: -0.7 (95% CI: -0.18 to 0.03, , I^2 = 69%)] • Reduction of diabetes-related complications: Based on very low certainty of evidence, there is no statistically significant difference between Insulin glargine and NPH insulin in terms of the following outcomes: ○ three step progression/worsening of retinopathy from baseline [RR: 1.03 (95% CI: 0.60 to 1.77, I^2 = 54%)], ○ risk of fatal myocardial infarction [RR: 2.76 (95% CI: 0.29 to 26.48, I^2 not reported)]	hyperglycemia (blood glucose ≥250 mg/dL [13.9 mmol/L], A1C ≥8.5% [69 mmol/mol]) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while metformin is initiated and titrated. *(Level of Evidence: B)* • In patients with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued. *(Level of Evidence: A)* • If glycemic targets are no longer met with metformin (with or without basal insulin), glucagon-like peptide 1 receptor agonist (GLP1-RA) therapy approved for youth with type 2 diabetes should be considered in children 10 years of age or older if they

	• All-Cause Mortality: Based on low certainty of evidence, there is no statistically significant difference between insulin glargine and NPH insulin in terms of reducing the odds of all-cause mortality [Peto OR: 1.06 (0.62 to 1.82, I^2 = 28%)], • Quality of Life (QoL): Based on very low quality of evidence from three trials, there is no statistically significant difference between insulin glargine, detemir and NPH insulin in terms of health-related QoL scores of patients in the Well-Being Questionnaire (W-BQ22), EuroQol 5 (EQ-5) instrument or any other subscale. ○ Massi 2003 used the Well-being Questionnaire (W-BQ22). The difference between trial start and trial end for total score was 1.0 (95% CI −45.0 to 32.0) for glargine and 0.0 (95% CI −25.2 to 46.2) for NPH (P = 0.40). ○ Rosenstock 2001 used the W-BQ22. The difference between trial start and trial end for total score was 0.5 (95% CI −22.0 to 36.0) for glargine and 0.0 (95% CI −37.0 to 39.0) for NPH (P = 0.25). ○ Hermanns 2015 used the EuroQol 5 (EQ-5) instrument. The difference between trial start and trial end for EQ-5 descriptive was −0.009 (SD 0.1727) for glargine and 0.001 (SD 0.1606) for NPH (P = 0.62). The difference between trial start and trial end for EQ-5 Visual Analogue Scale (VAS) was −0.0 (SD 0.1646) for glargine and 0.009 (SD 0.1655) for NPH (P = 0.64). *Safety outcomes:* • Severe Hypoglycemia: Based on very low certainty of evidence, there is no statistically significant difference between insulin glargine and NPH insulin terms of risk of severe hypoglycemia [RR: 0.68 (95% CI: 0.46 to 1.01, I^2 = 17%)]. There was a significant reduction in hypoglycemia episodes associated with insulin glargine or insulin detemir as compared with NPH insulin. • Serious Hypoglycemia *(Events and Adverse Events)*: Based on low certainty of evidence, no significant differences between insulin	have no past medical history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. *(Level of Evidence: A)* • Patients treated with metformin, a GLP1-RA, and basal insulin who do not meet glycemic targets should be moved to multiple daily injections with basal and pre meal bolus insulins or insulin pump therapy. *(Level of Evidence: E)* • In patients initially treated with insulin and metformin who are meeting glucose targets based on blood glucose monitoring, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days. *(Level of Evidence: B)* *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*

	glargine or insulin detemir and NPH insulin were found in terms of risk of serious hypoglycemia [RR: 0.75 (95% CI: 0.52 to 1.09, I^2 = 0%)]. ● Serious adverse events: Based on moderate certainty of evidence, there is no statistically significant difference between insulin glargine and NPH insulin [RR: 0.98 (95% CI: 0.87 to 1.10, I^2 = 0%)]. ● All adverse events: Based on moderate certainty of evidence, Insulin glargine and NPH insulin have no statistically significant difference in terms of all adverse events [RR: 1.01 (95% CI: 0.98 to 1.03, I^2=0%)]. *Czech M et. al., 2015 [Systematic Review of 76 Observational Studies]* *Interventions: Long-acting insulin analogues (insulin glargine and detemir only)* *Comparator: NPH Insulin, sulfonylureas in monotherapy, insulin pump* ● T2DM Annual Probability Of One Or More Severe Hypoglycaemia: Based on medium to good quality of evidence, the event per patient for basal-bolus insulin analogues was at 4.8% (95% CI 1.2% to 27.0%) and 31.40 % (7.44 %–99.64 %) for the basal human insulin arm. Pooled T1DM and T2DM: *Singh K et. al., 2015 [Systematic Review and Meta-Analysis of 23 Studies]* *Interventions: Rapid- and Long-Acting Insulin Analogs, Basal-bolus Insulin Analogs (Insulin Glargine, Insulin Detemir)* *Comparator: Regular or NPH Non-Analog Insulins* *Efficacy outcomes:* ● Reduced Days Spent In Hospital: Based on low quality of evidence, a meta-analysis of four randomized trials comparing analogue basal-bolus routine regimens with human insulin basal bolus regimens estimated that analogues reduced days spent in hospital by 0.9 days (MD, −0.90, 95% CI −1.45 to −0.34 days) *Safety outcomes:*	*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* *Level of evidence: B* ● *Supportive evidence from well-conducted cohort studies* ○ *Evidence from a well-conducted prospective cohort study or registry* ○ *Evidence from a well-conducted meta-analysis of cohort studies* ● *Supportive evidence from a well-conducted case-control study* *Level of evidence: C* ● *Supportive evidence from poorly controlled or uncontrolled studies* ○ *Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results* ○ *Evidence from*

	● Postoperative Complications: Based on very low quality of evidence, one randomized controlled trial found lower rates of postoperative complications (RR 0.69, 95% CI 0.52 to 0.93). ● Hypoglycemia Events: Based on very low quality of evidence, comparing long-acting insulin analogues with human NPH insulin in hospitalized patients found a reduction in hypoglycemia events *Lv S, Wang J, Xu Y 2015 [Systematic Review of 8 Observational Studies and 1 RCT] - study inaccessible* *Safety outcomes:* ● Maternal Outcomes and Safety: No significant differences in fetal, neonatal or maternal outcomes for insulin detemir. *Allocati et al., 2020 [Systematic Review]* *Interventions: Insulin Analogs (Insulin Detemir, Insulin Glargine and Insulin Degludec) and Biosimilars* *Comparator: NPH Insulin and Biosimilars* *Safety outcomes:* ● Safety signals: Based on very poor evidence, insulin biosimilars indicated safety signals when switching from originator to biosimilar insulin and insulin analogues. In regard to biosimilars, evidence to date indicates no safety signals when switching patients from originator to biosimilar insulin *Karlstad et al., 2013 [Systematic Review and Meta-Analysis of 34 studies]* *Interventions: Insulin Analogs (Insulin Glargine) , Exogenous human insulin* *Comparator: Other Types Of Insulin, Non-Insulin Antidiabetic Drugs* *Quality Assessment: According to the scores attained using the Newcastle-Ottawa Scale (NOS), the NOS scores of the 34 studies ranged from 7 to 9 (high quality of evidence) and 4 to 6 (high risk of bias).* ● Risk of cancer:	*observational studies with high potential for bias (such as case series with comparison with historical controls)* ○ *Evidence from case series or case reports* ● *Conflicting evidence with the weight of evidence supporting the recommendation* *Level of evidence: E* *Expert consensus or clinical experience*

	○ Insulin exposure in general was associated with an increased risk of cancer in the pancreas, (RR 2.58, 95% CI 2.05 to 3.25), liver (RR 1.84, 95% CI 1.32 to 2.58), kidney (RR 1.38, 95% CI 1.06 to 1.79), stomach (RR 1.65, 95% CI 1.02 to 2.68) and respiratory system (RR 1.30, 95% CI 1.14 to 1.47), and decreased risk of prostate cancer (RR 0.80, 95% CI 0.73 to 0.88) as compared to no insulin. ○ Insulin glargine exposure was associated with a decreased risk of colon cancer (RR 0.71, 95% CI 0.56 to 0.91) and a marginally significant increased risk of breast cancer (RR 1.14, 95% CI 1.01 to 1.29) compared with users of non-glargine insulin. *Home et al., 2009 [Meta-Analysis]* *Interventions: Insulin Glargine* *Comparator: NPH insulin* *Quality assessment: not performed* ● Risk of cancer: There was no statistically significant difference between Insulin glargine and other active comparators such as NPH insulin or oral antidiabetics in terms of cancer events(RR 0.90, 95% CI 0.60 to 1.36). *Djegaard A. et al., 2009 [Meta-Analysis]* *Interventions: Insulin Detemir* *Comparator: NPH Insulin, Insulin Glargine* *Quality assessment: not performed* ● Odds of having cancer: The meta-analysis compared insulin detemir with NPH insulin and found more cases of cancer in the NPH insulin arm (OR 2.44 95% CI 1.01 to 5.89). Meanwhile, there was no statistically significant difference in the odds of when insulin glargine arm was compared with insulin detemir (OR=1.47, 95%CI: 0.55–3.94).	

Costing analysis

A. Insulin Glargine and Detemir for Type 1 Diabetes Mellitus

For the costing analysis, the direct medical cost items included were the: (1) cost of the drug regimen; and the (2) cost of other direct medical cost items *[cost of administration, cost of severe hypoglycemia management]* at a third-party payer/government perspective for one year. According to the Philippine College of Endocrinology, Diabetes, and Metabolism (PCEDM), the duration of insulin treatment for type 1 diabetes mellitus usually lasts for a lifetime. However, for this costing analysis the treatment cost for one year is assumed for the comparison between interventions and the comparator. Regimens and resource utilization were also consulted with the PCEDM. From these, the final costing outputs were the total cost of the treatment regimen per patient and for all expected users.

The unit costs of insulin analogues and their respective biosimilars were from the price offered by local distributors while the Drug Price Reference Index (DPRI) price was used for the comparator unit of NPH insulin. However, there were no price offers obtained from local manufacturers of insulin detemir biosimilars and insulin detemir innovator vials, hence these delivery systems were not included in the analysis. Lastly, the cost of blood glucose monitoring was omitted in this analysis since this cost will be uniform across all interventions and comparators and will not constitute the judgment on incremental cost. The table below indicates the unit costs and assumptions used in the analysis.

Overall, the total cost of treatment including the drug regimen and administration per patient ranged from ₱6,093.68 for the NPH Insulin vial up to ₱28,660.10 for Insulin Glargine pen biosimilars per year. However, if the patient experiences severe hypoglycemia during treatment, this will incur an additional cost due to hospitalization with a PhilHealth case rate equivalent to ₱4,000.00. This resulted in a total cost ranging from ₱10,093.68 for NPH insulin vial to ₱22,566.43 for Glargine pen biosimilars. Furthermore, the transition probabilities of experiencing severe hypoglycemia were derived from the results of randomized clinical trials (i.e. Home et al., 2005, Ratner et al., 2000, Raskin et al., 2000, and Rosenstock et al., 2000). From this, the results showed that T1DM patients on Insulin Glargine, Insulin Detemir, and NPH have a 6.16%, 8.50%, and 12.77% probability of experiencing severe hypoglycemia respectively.

The total number of users were extrapolated using the T1DM prevalence in the Philippines from the Global Burden of Disease study (2010 - 2019). From this, the computed total costs incurred to the government are as follows : Insulin Glargine vial: ₱1.39 B, Insulin Glargine pen: ₱2.10 B, Insulin Detemir pen: ₱2.56 B, Insulin Glargine biosimilar Vial: ₱1.35 B, Insulin Glargine pen: ₱3.23 B, and NPH Insulin ₱7.37 B.

Parameters	Intervention			Comparators			Remarks	Reference/s
	Insulin Glargine Innovator		*Insulin Detemir Innovator*	*Insulin Glargine Biosimilars*		*NPH insulin Innovator/biosimilar*		
Delivery System	*Vial*	*Pen*	*Pen*	*Vial*	*Pen*	*Vial*		
Part 1: Cost of Drug Regimen								
Unit cost of Drug per International Units (IU)	₱1.04	₱1.37	₱1.80	₱1.00	₱2.47	₱0.0790	-	Local Distributor submissions 2022 DPRI, 2021
Dosing regimen	25 IU once daily	25 IU once daily	25 IU once daily	25 IU once daily	25 IU once daily	25 IU per day (15 IU before breakfast and 10IU before dinner)	Recommended dosing regimen is 0.5 IU per kg per day, while the average weight of a Filipino T1DM patient is 50 kg.	PCEDM, 2022
Duration of Treatment	365	365	365	365	365	365	Lifetime treatment For the purpose of this analysis, one year of treatment will be	PCEDM, 2022

							assumed.	
Total Cost of Drug Regimen per year	₱9,526.50	₱12,490.30	₱16,465.76	₱9,125.00	₱22,546.35	₱720.8750		
Part 2: Cost of Administration								
Unit Cost of Syringe	₱7.36	₱16.75	₱16.75	₱7.36	₱16.75	₱7.36	Syringe, 100U or 50U are used for vials and Needle G 4mm are used for pens DOH Medical Device Unit [MDU] database (average cost from procurement of hospitals)	DOH MDU, 2022 MEDEXPRESS 2022
Frequency of use	1	1	1	1	1	2		PCEDM, 2022
Duration of Use	365	365	365	365	365	365	Lifetime treatment For the purpose of this analysis, one year of treatment will be assumed.	PCEDM, 2022
Total Cost of Other Costs	₱2,686.40	₱6,113.75	₱6,113.75	₱2,686.40	₱6,113.75	₱5,372.80		
Part 3: Cost of Severe Hypoglycemia Management								
Cost of Hospitalization due to Severe Hypoglycemia	₱ 4,000							PhilHealth Case Rate, 2022
Part 4.1: Total Cost of Treatment Regimen per patients who WILL NOT experience severe hypoglycemia								

Total Cost of Treatment Regimen per patient	₱12,212.90	₱18,604.05	₱22,579.51	₱11,811.40	₱28,660.10	₱6,093.68	Total Cost of Drug Regimen + Total Cost of Administration	
Incremental Cost of Treatment Regimen per Patient	₱6,119.23	₱12,510.38	₱16,485.83	₱5,717.73	₱22,566.43	NA	Difference between the cost of Intervention and the comparator (NPH insulin)	
Part 4.2: Total Cost of Treatment Regimen per patients who WILL experience severe hypoglycemia								
Total Cost of Treatment Regimen per patient	₱16,212.90	₱22,604.05	₱26,579.51	₱15,811.40	₱32,660.10	₱10,093.68	Total Cost of Drug Regimen + Total Cost of Administration + Cost of hospitalization due to severe hypoglycemia	
Incremental Cost of Treatment Regimen per Patient	₱6,119.23	₱12,510.38	₱16,485.83	₱5,717.73	₱22,566.43	NA	Difference between the cost of Intervention and the comparator (NPH insulin)	
Part 4: Total Cost of Treatment Regimen for all users								
Number of Users	111,628	111,628	111,628	111,628	111,628	111,628	Global Burden of Disease Study 2010 to 2019 extrapolation	Global Burden of Disease Study (GBD), 2019
Proportion who are likely to experience severe hypoglycemia	6.16%	6.16%	8.50%	6.16%	6.16%	12.77%	These transition probabilities were computed from the pooled rates of severe hypoglycemia in clinical trials.	Home et al., 2005, Ratner et al., 2000, Raskin et al., 2000, and

								Rosenstock et al., 2000
EXPECTED NUMBER OF USERS WHO WILL EXPERIENCE SEVERE HYPOGLYCEMIA	6,875	6,875	9,494	6,875	6,875	14,250	[redacted]	
EXPECTED NUMBER OF USERS WHO WILL NOT EXPERIENCE SEVERE HYPOGLYCEMIA	104,753	104,753	102,134	104,753	104,753	97,378		
Total Cost of Treatment Regimen for all users	₱1,390,801,601.20	₱2,104,232,893.40	₱2,558,481,356.23	₱1,345,982,959.20	₱3,226,770,107.92	₱737,224,752.90		
Incremental Cost of Treatment Regimen for all users	₱653,576,848.30	₱1,367,008,140.50	₱1,821,256,603.33	₱608,758,206.30	₱2,489,545,355.02	NA		

B. Insulin Glargine and Detemir for Type 2 Diabetes Mellitus

For the costing analysis, the direct medical cost items included were the: (1) cost of the drug regimen; and the (2) cost of other direct medical cost items *[cost of administration, cost of severe hypoglycemia management]* at the third-party payer/government perspective for one year. From these, the final costing outputs were the total cost of the treatment regimen per patient and for all expected users. Regimens and resource utilization were consulted with the Philippine College of Endocrinology, Diabetes, and Metabolism (PCEDM).

The unit costs of insulin analogues and their respective biosimilars were from the price offered by local distributors while the DPRI price was used for the comparator unit of NPH insulin. However, there were no price offers obtained from local manufacturers of insulin detemir biosimilars and insulin detemir innovator vials, hence these delivery systems were not included in the analysis. Lastly, the cost of blood glucose monitoring was omitted in this analysis since this cost will be uniform across all interventions and comparators and will not constitute the judgment on incremental cost. The table below indicates the unit costs and assumptions used in the analysis.

The total cost of treatment which includes the drug regimen and administration per patient ranges from ₱733.50 for NPH Insulin vial up to ₱7,731.25 for Insulin Glargine pen per year. However, if the patient experiences severe hypoglycemia during treatment, this will incur an additional cost due to hospitalization with a PhilHealth case rate equivalent to ₱4,000.00. This resulted in a total cost ranging from ₱4,733.50 for NPH insulin vial up to ₱7,731.25 for Insulin Glargine pen biosimilars. Furthermore, the transition probabilities of experiencing severe hypoglycemia were derived from the results of randomized clinical trials cited in the systematic review of Semlitsch et al., 2020. From these, the results showed that T2DM patients on Insulin Glargine, Insulin Detemir, and NPH have a 3.07%, 0.87%, and 3.21% probability of experiencing severe hypoglycemia respectively.

The total number of users were extrapolated using the T2DM prevalence in the Philippines from the Global Burden of Disease Study (2010-2019). From this, the computed total incurred costs for the government are as follows: Insulin Glargine vial: ₱1.54 B, Insulin Glargine pen: ₱2.56 B, Insulin Detemir pen: ₱2.84 B Insulin Glargine biosimilars vial: ₱1.51 B, Insulin Glargine pen: ₱3.45 B, NPH Insulin ₱772.00 million.

Parameters	Intervention			Comparators			Remarks	Reference/s
	Insulin Glargine Innovator		*Insulin Detemir Innovator*	*Insulin Glargine Biosimilars*		*NPH insulin Innovator*		
Delivery System	*Vial*	*Pen*	*Pen*	*Vial*	*Pen*	*Vial*		
Part 1: Cost of Drug Regimen								
Unit cost of Drug per IU	₱1.04	₱1.37	₱1.80	₱1.00	₱2.47	₱0.0790		Local Distributor submissions 2022

								DPRI, 2021
Dosing regimen	10 IU once daily	10 IU once daily	10 IU once daily	10 IU once daily	10 IU once daily	10 IU once daily	Recommended dosing regimen is 0.2 IU per kg per day, while the average weight of a Filipino T2DM patient is 50 kg.	PCEDM, 2022
Duration of Treatment	90	90	90	90	90	90	The average duration of treatment of insulin for T2DM patients is 3 months. This may last longer until improvement of glucose levels.	PCEDM, 2022
Total Cost of Drug Regimen per year	₱939.60	₱1,231.92	₱1,624.02	₱900.00	₱2,223.75	₱71.1000		
Part 2: Cost of Administration								
Unit Cost of Syringe/Needle	₱7.36	₱16.75	₱16.75	₱7.36	₱16.75	₱7.36	Syringe, 100U or 50U are used for vials and Needle G 4mm are used for pens DOH Medical Device Unit [MDU] database (average cost from procurement of hospitals)	DOH MDU, 2022 MEDEXPRESS 2022
Frequency of	1	1	1	1	1	1		PCEDM, 2022

use								
Duration of Use	90	90	90	90	90	90	Lifetime treatment For the purpose of this analysis, one year of treatment will be assumed.	PCEDM, 2022
Total Cost of Other Costs	₱662.40	₱1,507.50	₱1,507.50	₱662.40	₱1,507.50	₱662.40		
Part 3: Cost of Severe Hypoglycemia Management								
Cost of Hospitalization due to Severe Hypoglycemia	₱ 4,000							PhilHealth Case Rate, 2022
Part 4.1: Total Cost of Treatment Regimen per patients who WILL NOT experience severe hypoglycemia								
Total Cost of Treatment Regimen per patient	₱1,602.00	₱2,739.42	₱3,131.52	₱1,562.40	₱3,731.25	₱733.50	Total Cost of Drug Regimen + Total Cost of Administration	
Incremental Cost of Treatment Regimen per Patient	₱868.50	₱2,005.92	₱2,398.02	₱828.90	₱2,997.75	NA	Difference between the cost of Intervention and the comparator (NPH insulin)	
Part 4.2: Total Cost of Treatment Regimen per patients who WILL experience severe hypoglycemia								
Total Cost of Treatment Regimen per patient	₱5,602.00	₱6,739.42	₱7,131.52	₱5,562.40	₱7,731.25	₱4,733.50	Total Cost of Drug Regimen + Total Cost of Administration + Cost of hospitalization due to severe	

							hypoglycemia	[redacted]
Incremental Cost of Treatment Regimen per Patient	₱868.50	₱2,005.92	₱2,398.02	₱828.90	₱2,997.75	NA	Difference between the cost of Intervention and the comparator (NPH insulin)	
Part 4: Total Cost of Treatment Regimen for all users								
Number of Users	895,603	895,603	895,603	895,603	895,603	895,603	Global Burden of Disease Study 2010 to 2019 extrapolation	Global Burden of Disease Study (GBD), 2019
Proportion who are likely to experience severe hypoglycemia	3.07%	3.07%	0.87%	3.07%	3.07%	3.21%	These transition probabilities were computed from the pooled rates of severe hypoglycemia in clinical trials included in the systematic review of Semlitsch et al..	Semlitsch et al., 2020
EXPECTED NUMBER OF USERS WHO WILL EXPERIENCE SEVERE HYPOGLYCEMIA	27,520	27,520	7,795	27,520	27,520	28,770	[redacted]	
EXPECTED NUMBER OF USERS WHO WILL NOT EXPERIENCE	868,083	868,083	887,808	868,083	868,083	866,833		

SEVERE HYPOGLYCEMIA							
Total Cost of Treatment Regimen for all users	₱1,544,832,656.15	₱2,563,509,420.41	₱2,835,777,793.33	₱1,509,366,777.35	₱3,451,795,343.90	₱772,001,411.30	
Incremental Cost of Treatment Regimen for all users	₱772,831,244.85	₱1,791,508,009.11	₱2,063,776,382.03	₱737,365,366.05	₱2,679,793,932.60	NA	

Budget impact analysis

A. Insulin Glargine and Detemir for Type 1 Diabetes Mellitus

The budget impact analysis over a 3-year horizon was performed using data from sources indicated in Annex 2.A. The incidence of T1DM in the Philippines from 2023-2024 was estimated by projecting the Global burden of disease data from 2010 to 2019. Lastly, lifetime insulin treatment is assumed for T1DM patients based on consultation with PCEDM, hence, the number of patients .

The total cost of insulin analogue treatment for all expected users from 2022 to 2024 ranged from ₱1.44 B (insulin glargine biosimilars) to ₱3.44 B (insulin glargine biosimilar pen). All long-acting insulin analogues had a relatively higher budget impact as compared to NPH insulin. Insulin glargine biosimilar vials were relatively cheaper than its innovator counterparts. However, insulin glargine biosimilar pens were more expensive than the innovator.

Parameter/Year	Intervention					Comparator	Remarks	Reference/s
	Insulin Glargine Innovator		*Insulin Detemir Innovator*	*Insulin Glargine Biosimilars*		*NPH insulin Innovator/biosimilar*		
Delivery System	*Vial*	*Pen*	*Pen*	*Vial*	*Pen*	*Vial*		
For patients who WILL experience severe hypoglycemia								
Proportion of total users who are expected to experience Severe Hypoglycemia	6.16%	6.16%	8.50%	6.16%	6.16%	12.77%	These transition probabilities were computed from the pooled rates of severe hypoglycemia in clinical trials.	Home et al., 2005, Ratner et al., 2000, Raskin et al., 2000, and Rosenstock et al., 2000
Cost of treatment per patient	₱16,212.90	₱22,604.05	₱26,579.51	₱15,811.40	₱32,660.10	₱10,093.68		
Number of patients (2022)	6,875	6,875	9,494	6,875	6,875	14,250	Projected prevalence of T1DM in the Philippines in 2022.	Global Burden of Disease

							Estimated using the GBD data from 2010 to 2019	Study 2019
Number of patients (2023)	7,106	7,106	9,813	7,106	7,106	14,728	Projected incidence of T1DM in the Philippines from 2023-2025. Estimated using the GBD data from 2010 to 2019	Global Burden of Disease Study 2019
Number of patients (2024)	7,340	7,340	10,136	7,340	7,340	15,214		
For patients who WILL NOT experience severe hypoglycemia								
Proportion of total users who are expected to NOT experience Severe Hypoglycemia	93.84%	93.84%	91.50%	93.84%	93.84%	87.23%		
Cost of treatment per patient	₱12,212.90	₱18,604.05	₱22,579.51	₱11,811.40	₱28,660.10	₱6,093.68		
Number of patients (2022)	104,753	104,753	102,134	104,753	104,753	97,378	Projected prevalence of T1DM in the Philippines in 2022. Estimated using the GBD data from 2010 to 2019	Global Burden of Disease Study 2019
Number of patients (2023)	108,264	108,264	105,557	108,264	108,264	100,642	Projected incidence of T1DM in the Philippines from 2023-2025. Estimated using the GBD data from 2010 to 2019	Global Burden of Disease Study 2019
Number of patients (2024)	111,836	111,836	109,040	111,836	111,836	103,962		
Total Cost of Treatment Regimen for all users								
Total cost (2022)	₱1,390,801,601.20	₱2,104,232,893.40	₱2,558,481,356.23	₱1,345,982,959.20	₱3,226,770,107.92	₱737,224,752.90		
2023	₱1,437,426,273.00	₱2,174,773,248.50	₱2,644,249,876.42	₱1,391,105,218.00	₱3,334,940,217.71	₱761,939,284.75		
2024	₱1,484,844,570.40	₱2,246,516,262.80	₱2,731,479,485.13	₱1,436,995,406.40	₱3,444,956,574.17	₱787,075,811.80		
Total Cost of Treatment Regimen for all users in billions [B]								
2022	₱1.39 B	₱2.10 B	₱2.56 B	₱1.35 B	₱3.23 B	₱0.74 B		
2023	₱1.44 B	₱2.17 B	₱2.64 B	₱1.39 B	₱3.33 B	₱0.76 B		
2024	₱1.48 B	₱2.25 B	₱2.73 B	₱1.44 B	₱3.44 B	₱0.79 B		

TOTAL COST FOR 3 YEARS (in billion [B] ₱)	₱4.31 B	₱6.53 B	₱7.93 B	₱4.17 B	₱10.01 B	₱2.29 B		
Incremental Cost of Treatment for all users for 3 years	₱2.03	₱4.24	₱5.65	₱1.89	₱7.72	NA		

B. Insulin Glargine and Detemir for Type 2 Diabetes Mellitus

The budget impact analysis over a 3-year horizon was performed using data from sources indicated in Annex 2.B. The incidence of T2DM in the Philippines from 2023-2024 was estimated by projecting the Global burden of disease data from 2010 to 2019. Lastly, a three month insulin treatment is assumed for T2DM patients based on consultation with PCEDM as patients are expected to have better glycemic control afterwards.

The total cost of insulin analogue treatment for all expected users from 2022 to 2024 ranged from ₱1.71 B (insulin glargine biosimilars) to ₱3.91 B (insulin glargine biosimilar pen). All long-acting insulin analogues had a relatively higher budget impact as compared to NPH insulin. Insulin glargine biosimilar vials were relatively cheaper than its innovator counterparts. However, insulin glargine biosimilar pens were more expensive than the innovator.

Parameters/Year	Intervention					Comparator	Remarks	Reference/s
	Insulin Glargine Innovator		*Insulin Detemir Innovator*	*Insulin Glargine Biosimilars*		*NPH insulin Innovator/biosimilar*		
Delivery System	*Vial*	*Pen*	*Pen*	*Vial*	*Pen*	*Vial*		
For patients who WILL experience severe hypoglycemia								
Proportion of total users who are expected to	3.07%	3.07%	0.87%	3.07%	3.07%	3.21%		

experience Severe Hypoglycemia								
Cost of treatment per patient	₱5,602.00	₱6,739.42	₱7,131.52	₱5,562.40	₱7,731.25	₱4,733.50		
Number of patients (2022)	27,520	27,520	7,795	27,520	27,520	28,770	Projected prevalence of T1DM in the Philippines in 2022. Estimated using the GBD data from 2010 to 2019	Global Burden of Disease Study 2019
Number of patients (2023)	1,785	1,785	506	1,785	1,785	1,866	Projected incidence of T1DM in the Philippines from 2023-2025. Estimated using the GBD data from 2010 to 2019	Global Burden of Disease Study 2019
Number of patients (2024)	1,870	1,870	530	1,870	1,870	1,955		
For patients who WILL NOT experience severe hypoglycemia								
Proportion of total users who are expected to NOT experience Severe Hypoglycemia	96.93%	96.93%	99.13%	96.93%	96.93%	96.79%	These transition probabilities were computed from the pooled rates of severe hypoglycemia in clinical trials included in the systematic review of Semlitsch et al..	Semlitsch et al., 2020
Cost of treatment per patient	₱1,602.00	₱2,739.42	₱3,131.52	₱1,562.40	₱3,731.25	₱733.50		
Number of patients (2022)	868,083	868,083	887,808	868,083	868,083	866,833	Projected prevalence of T1DM in the Philippines in 2022. Estimated using the GBD data from 2010 to 2019	Global Burden of Disease Study 2019
Number of patients (2023)	56,287	56,287	57,566	56,287	56,287	56,206	Projected incidence of T1DM in the Philippines from 2023-2025. Estimated using the GBD data from 2010 to 2019	Global Burden of Disease Study 2019
Number of patients (2024)	58,968	58,968	60,308	58,968	58,968	58,883		
Total Cost of Treatment Regimen for all users								
2022	₱1,544,836,006.00	₱2,563,512,770.26	₱2,835,778,706.56	₱1,509,370,127.20	₱3,451,798,693.75	₱772,004,800.50		
2023	₱100,171,34	₱166,223,59	₱183,877,62	₱97,871,692.	₱223,821,15	₱50,059,812.		

	4.00	8.24	9.44	80	0.00	00		
2024	₱104,942,476.00	₱174,140,833.96	₱192,635,413.76	₱102,533,291.20	₱234,481,787.50	₱52,444,673.00		
Total Cost of Treatment Regimen for all users in billions								
2022	₱1.54 B	₱2.56 B	₱2.84 B	₱1.51 B	₱3.45 B	₱0.77 B		
2023	₱0.10 B	₱0.17 B	₱0.18 B	₱0.10 B	₱0.22 B	₱0.05 B		
2024	₱0.10 B	₱0.17 B	₱0.19 B	₱0.10 B	₱0.23 B	₱0.05 B		
TOTAL COST FOR 3 YEARS (in billion ₱)	₱1.75 B	₱2.90 B	₱3.21 B	₱1.71 B	₱3.91 B	₱0.87 B		
Incremental Cost of Treatment for all users for 3 years	₱0.88 B	₱2.03 B	₱2.34 B	₱0.84 B	₱3.04 B	NA		

Summary of cost-effectiveness evidence and recommendations of the WHO

WHO approved indication in the EML	Remarks on Cost-effectiveness from WHO Review for Essential Medicines listing
Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus patients who are at high risk of experiencing hypoglycemia with human insulin	Overall, the positive recommendation did not receive the support of all Committee members due to concerns about the differences in price and potential effect on the availability of human insulin. The WHO Expert Committee recognized the current high price of insulins, both human and its analogues, as a barrier to access. Despite these circumstances, the Committee still included LAIs in the Core list of the WHO EML and highlighted the following actions that can be undertaken to remove or mitigate these barriers: ● Including price negotiations, pooled procurement, competitive tendering, support of technology transfer between manufacturers and the increased use of biosimilars. ● WHO continues working on policies and actions that will lead to relevant and rapid price reductions at the country level, based on systematic evaluation of evidence and implementation experiences of countries. ● WHO to evaluate the effect of the EML listing of insulin analogues on the global availability, accessibility and price of insulins over a multiyear period. The Committee also highlighted the importance of commitment and action from Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally. The Committee also considered that insulin could be a priority medicine for the proposed Working Group on high-priced essential medicines in close coordination with the WHO pricing team. The following studies were included in the WHO review: Cost-Effectiveness Studies Most available cost-effectiveness (CE) studies focus on high-income settings. In all studies, procurement costs for long-acting insulin analogues are considerably greater than for human insulins. Some cost–effectiveness analyses have found that, despite greater procurement cost, insulin analogues are more cost-effective than human insulins because of savings resulting from (assumed/ modeled) health benefits such as lower rates of hypoglycaemia.

	Shafie et al, 2017 *[Systematic review of 50 studies on insulin analogue; 21 studies specific to LAIs as intervention]* *Intervention: Short- or long-acting and biphasic insulin analogues* *Comparator: NPH insulin* *Quality assessment: 15 out of 50 studies met the CHEERS guidelines* Of the 21 studies on long-acting insulin analogues, five concluded that LAIs were dominant over NPH insulin (i.e. had both lower cost and greater benefits) while one study concluded that LAIs were dominated by NPH insulin (i.e. had both greater cost and lesser benefits). The incremental cost-effectiveness ratios (ICER) for LAIs compared to NPH insulin computed in the other studies ranged from US$ 661 to US$ 361,721 per quality adjusted life years (QALY). The WHO noted that this large range in the ICER values is caused by different underlying assumptions used across studies, particularly regarding: (i) the baseline characteristics of patients, complication frequency and severity, use and cost of self-monitoring blood glucose test strips and devices (e.g. pen, cartridge, vial), and (ii) the different (estimated) magnitudes of benefit in reducing hypoglycemia events and reductions in HbA1c. There was one study included in the systematic review that assessed the cost-effectiveness of insulin detemir as compared to oral antidiabetics in T2DM patients from three Lower Middle Income Countries (LMICs) - India, Indonesia, and Algeria. The study (Home et al., 2015) used the CORE Diabetes Model which is based on a network of Markov sub-models that simulate complications often associated with diabetes (e.g. cardiovascular disease, eye disease, hypoglycemia, ulcers, amputation, stroke, lactic acidosis, nephropathy, neuropathy, ketoacidosis, and mortality). Costs collected from a public health payer perspective include those associated with diabetes management (annual costs for other medications and screening tests) and relevant comorbid medical conditions. Insulin detemir was considered cost-effective in all these LMICs with 30-year ICER values of 0.48 (India), 0.12 (Indonesia), and 0.88 (Algeria) Gross Domestic Product (GDP) per QALY which are all below the WHO - Choosing Interventions that are Cost Effective (CHOICE) threshold of <3.0 GDP per capita. Cost-effectiveness was maintained after conducting sensitivity analyses in the 1-year analysis in these LMICs.

	Lee et al.2019 *[Cost-effectiveness Cohort study]* *Intervention: long-acting insulin analogues (LAIs)* *Comparator: intermediate/long-acting human insulin (ILAHI)* *Quality Assessment: The reporting of the study follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement* This cost-effectiveness study conducted in Taiwan, a high income country (HIC) in Asia concluded that the greater pharmaceutical costs of LAIs in T1DM patients could be substantially offset by savings from averted hypoglycemia or diabetes-related complications. The study utilized actual T1DM cases from 2004 to 2013 with over 10 years of follow-up. For each study patient both direct medical costs paid by Taiwan's NHI program (eg, costs of emergency department visits, hospitalization, outpatient care, laboratory tests and medications) and the out-of-pocket expense paid by patients were considered. Results from the study showed that from a third-party payer and healthcare sector perspective, using LAIAs instead of ILAHI saved British pounds (£) 6,924 to £ 7,116 per case of hypoglycemia requiring medical assistance prevented, £ 5,346 to £ 5,508 per case of out-patient hypoglycaemia prevented, and £ 3,570 to £ 3,680 per case of any diabetes-related complications prevented. Overall, based on the base-case and sensitivity analysis results, LAIAs are deemed highly cost-effective with an almost 100% likelihood of falling below the threshold of one GDP per capita in Taiwan (£ 13,981). Lau et al., 2019 *[Cost-effectiveness Cohort study]* *Intervention: Insulin Glargine* *Comparator: Neutral Protamine Hagedorn (NPH) insulin* *Quality Assessment: Not Performed* The study concluded that insulin glargine U100 is a cost-effective treatment for patients with T2DM compared to NPH insulin in Hong Kong, a high income region. The study was analyzed from a societal perspective which includes costs of insulin, costs related to diabetes complications and indirect costs such as time/opportunity costs (i.e. Lost work time, lost leisure time or productivity gains and losses) and community preferences. The

	cost-effectiveness threshold was set at the current willingness-to-pay (WTP) threshold of Hong Kong at HKD 343,312 with a discount rate of 3% both for costs and outcomes and a treatment horizon of 50 years (lifetime). The study utilized a semi-markov model to recognize patterns and make predictions and learn the statistics of the sequential data. Insulin glargine U100 resulted in an ICER of HKD 98,663 per Quality Adjusted Life Year (QALY) gained, which falls below the threshold (HKD 343,312 per QALY gained). The cost-effectiveness of insulin glargine was mainly driven by the significantly lower rates of hypoglycaemia of insulin glargine U100 than NPH insulin. The incremental gains in QALY and costs were 0.217 years and HKD 21,360 respectively. Total costs of treating diabetes amounted to HKD 762,136 for a patient receiving glargine U100 and HKD 740,776 for a patient using NPH. Following a probabilistic sensitivity analysis considering a range of values for both direct and indirect costs, as well as treatment effects and transition probabilities, the probability of glargine U100 being a cost-effective treatment at the defined threshold compared to NPH resided at approximately 75%. Shafie & Ng, 2020 *[Cost-effectiveness Cohort study]* *Intervention: Insulin Glargine & Insulin Detemir* *Comparator: Neutral Protamine Hagedorn (NPH) insulin* *Quality Assessment: Not Performed* The study analyzed the cost-effectiveness of insulin Detemir and insulin Glargine using two-stage simulation modeling from a third-party payer perspective in Malaysia, an upper middle income country in Asia. The study estimated the lifetime health benefits of T2DM patients, as well as the long-term patient costs for diabetes related complications and the estimated costs and benefits generated from hypoglycemia for a 40-year time horizon and an annual discount rate of 3% applied to both costs. The acceptable threshold was set at RM 29,080/ QALY based on a previous local study. The total cost for using NPH insulin, insulin Detemir and insulin Glargine was RM 33,182 (US$ 7887), RM 39,209 (US$9320) and RM 38,051 (US$ 9045) respectively. Even though LAIA has higher therapy cost compared to NPH insulin, the ICERs for insulin Detemir (i.e.Dominant) and insulin Glargine (i.e. RM 3,732) over

	NPH insulin. Both insulin detemir and glargine remained well within the threshold and were regarded as the dominant and cost-effective options respectively. The cost may have been offset by the total cost of diabetes-related complications and managing severe hypoglycemia. The net cost difference (without accounting for hypoglycemia) was RM 4,868 for insulin Glargine and RM 6,026 for insulin Detemir while the savings from preventing severe hypoglycemia was RM 4,377 for insulin glargine and RM 12,753 for insulin Detemir. The total additional QALY gained from insulin Glargine was 0.1317 and from insulin Detemir was 0.8376. Cazarim et al., 2017 [*Cost-effectiveness study*] *Intervention: insulin analogs aspart, lispro, glargine and detemir* *Comparator: human insulin* *Quality Assessment: Not performed* This study conducted in Brazil, an upper middle income country, concluded that both insulin glargine and detemir are both dominant over NPH insulin in terms of percent reduction in HbA1c levels. The study utilized a decision tree model from a healthcare sector perspective - Brazilian Public Health System (BPHS). Unit price of insulins and its analogues were extracted from the Brazil Ministry of health while the clinical results on reduction of HbA1c levels were extracted from the meta-analysis of Sanches et al. 2013. Given the best-case scenario wherein there was a minimum difference in cost and maximum effectiveness, the ICER values of insulin aspart (R$ 1,768.59 per %HbA1c reduction), lispro (R$ 3,308.54 per %HbA1c reduction), glargine (R$ 11,718.75 per %HbA1c reduction), and detemir (R$ 2,685.22 per %HbA1c reduction) were less than the ICER threshold of R$ 86,628.00 per %HbA1c reduction (three times the per capita GDP of the year 2016). However, for all worst-case scenarios wherein the minimum effectiveness was assumed, insulins lispro, glargine and detemir were not cost-effective as they were dominated by human insulin with the exception of insulin aspart whose ICER values still fall below the ICER threshold. The sensitivity analysis results of the study showed that the most cost effective fast-acting insulin analog was aspart, R$ 3,066.98 [95% CI: 2339.22; 4418.53] per %HbA1c reduction and the most cost effective long-acting insulin was detemir, R$ 6,163.97 [95%

	CI: 3919.29; 11401.57] per %HbA1c reduction. Overall, the WHO expert committee noted that neither detemir nor glargine was cost-effective, which might be in reference to the worst-case scenarios of the study. Other Pharmacoeconomic Studies In addition to the CE studies above, a cross sectional cost minimization study in France (Detournay et al., 2021) showed that the average weekly total cost of insulin glargine treatment is not significantly different with other basal insulins (i.e. NPH insulin, insulin degludec), except for detemir which costs higher. Lastly, a study in China (Liu et al., 2017) found that a month's supply of long-acting insulin analogues cost 4 to 16 days' wages for the lowest-paid government worker compared with 4–7 days only for other insulins (i.e. human insulin, rapid-acting insulin analogues.