

HEALTH TECHNOLOGY ASSESSMENT

Sitagliptin for Type 2 Diabetes with Chronic Kidney Disease



AHEAD-HPSR

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List of Abbreviations

Abbreviation	Definition
ADA	antidiabetic agent
AE	adverse event
BMI	body mass index
BUN	blood urea nitrogen
CBG	capillary blood glucose
CrCl	creatinine clearance
CKD	chronic kidney disease
CG	Cockcroft-Gault
DM	diabetes mellitus
DPP4	dipeptidyl peptidase-4
DPRI	Drug Price Reference Index
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FBS	fasting blood sugar
FEC	Formulary Executive Council
GLP	glucagon-like peptide
HbA1c	glycated hemoglobin
HGE	hypoglycemic event
ICER	incremental cost-effectiveness ratio
IDF	International Diabetes Federation
IFG	impaired fasting glucose

IGT	impaired glucose tolerance
NEDA	National Economic and Development Authority
NKTI	National Kidney and Transplant Institute
NPH	neutral protamine Hagedorn
OGTT	oral glucose tolerance test
PNF	Philippine National Formulary
PO	oral administration
QALY	quality-adjusted life year
RBS	random blood sugar
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
T1DM	type 1 diabetes mellitus
TZD	thiazolidinedione
UACR	urinary albumin-creatinine ratio

EXECUTIVE SUMMARY

In the face of growing demand for quality and effective healthcare, the Department of Health (DOH) recognizes the need to properly and efficiently allocate its finite resources and limited budget. In response to this need, DOH institutionalizes and spearheads health technology assessment (HTA) in the Philippines as an explicit, transparent, and accountable process of evaluating the clinical efficacy, safety, and cost-effectiveness of any health technology to support policy decisions, particularly on service coverage and procurement and reimbursement of health technologies. This process is being utilized as a basis for inclusion of drugs in the Philippine National Formulary (PNF) and to aid the development of DOH programs and Philippine Health Insurance Corporation (PhilHealth) benefit packages.

Sitagliptin for Adult Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease Health Technology Assessment Dossier presents the assessment of sitagliptin as an alternative treatment for adult patients with type 2 diabetes mellitus and chronic kidney disease stages 4 and 5. In this assessment, sitagliptin was compared to the drugs currently listed in the PNF for type 2 diabetes mellitus – NPH insulin and sulfonylureas. This assessment serves as an evidence to aid the policy decision on the inclusion of sitagliptin to the PNF.

I. INTRODUCTION carefully outlines the patient's journey and the current guidelines and standard of care. More importantly, this chapter identifies and explains the unmet need that provides the rationale for the assessment of sitagliptin. This chapter presents the implications of the renal function of patients with chronic kidney disease in the treatment of type 2 diabetes mellitus.

II. PRODUCT INFORMATION presents the pharmacologic information of the drug of interest, sitagliptin, and the comparators, NPH insulin and sulfonylureas. In this chapter, the indication, mechanism of action, dosage, route of administration, contraindications, adverse effects, and possible drug interactions of sitagliptin were enumerated and were compared with NPH insulin and sulfonylureas. This chapter also explains the possible implications of using these type 2 diabetes mellitus treatments to patients with chronic kidney disease. Treatment compliance, as sourced from existing literature and studies, is also presented in this chapter.

III. COMPARATIVE CLINICAL EFFICACY AND SAFETY OF NPH INSULIN, SULFONYLUREA, AND SITAGLIPTIN IN T2DM CKD PATIENTS presents the review of existing literature and studies to provide evidence supporting and comparing the efficacy of sitagliptin, NPH insulin, and sulfonylurea. In this chapter, the methods done to gather and to review evidence is briefly outlined, including the research question and objectives, eligibility

criteria, the search strategy, the data collection process and data items, and the planned statistical analyses. The results of the said review are also presented and discussed in this chapter; these include the studies that were selected and their characteristics, the relevant outcomes gathered from these studies, and a brief discussion on the risk of bias. A conclusion is also provided at the end of this chapter.

IV. ECONOMIC VALUE provides the methods and the results of the economic evaluation of sitagliptin in comparison to sulfonylurea and NPH insulin. In this chapter, the rationale of the assessment is presented. Additionally, the model structure and parameters are also provided and discussed. The results of the economic evaluation include results of the cost-effectiveness analysis, deterministic and probabilistic sensitivity analyses, and budget impact analysis.

V. OPINION OF THE HTA STUDY GROUP provides the limitations that were identified during the assessment and how these were addressed or compensated for. Finally, an overall conclusion of the assessment is provided.

I. INTRODUCTION

1.1. Chapter Summary

- Diabetes mellitus causes 4.96 million deaths worldwide and affects 415 million diagnosed patients, according to the International Diabetes Federation.
- Chronic kidney disease, which further lowers the quality of life of a diabetic patient, is one of the most serious complications of having diabetes mellitus.
- Currently, there is a lack of a Philippine clinical practice guideline on the management of type 2 diabetes mellitus with chronic kidney disease.
- Medications prescribed by doctors in public hospitals and health facilities is limited to drugs listed in the Philippine National Formulary. The current version of the Philippine National Formulary has only 2 medications that are appropriate for stages 4 and 5 of chronic kidney disease: gliclazide and NPH insulin.
- In the Philippine setting, the patients experience several constraints while being diagnosed with chronic kidney disease, which are the inability to pay for the necessary medications and diagnostic and laboratory examinations and non-compliance and non-adherence to the medication due to adverse events.
- Treatment of type 2 diabetes mellitus poses an important challenge in people with chronic kidney diseases due to several factors, such as the severity of kidney dysfunction. Considering the potential benefits of sitagliptin in comparison with the drugs currently listed in the Philippine National Formulary, which includes its better safety profile, sitagliptin may prove as a cost-effective intervention in type 2 diabetes mellitus patients with chronic kidney disease stage 4 and 5.

1.2. Definition and clinical features of diabetic patients with chronic kidney disease

1.2.1. Diabetes mellitus

Diabetes mellitus (DM) is a chronic disease that occurs either when the pancreas does not produce enough insulin, a hormone responsible for regulating blood glucose, or when the body cannot effectively use the insulin it produces; the disease is characterized mainly by hyperglycemia¹. According to the latest Diabetes Atlas published by the International Diabetes Federation (IDF)² in 2015, an estimated 415 million adults globally has DM. It was also estimated that 1 in 11 adults has DM (7.2% to 11.4%), and approximately 1 in 2 adults with DM (46.5%) are undiagnosed. More than 4.96 million deaths worldwide are diabetes-related. In the Philippines, the national prevalence in 2008 of diagnosed DM among those with age of 20 to 79 years, according to the National Nutrition Survey, is 7.2%³. Furthermore,

approximately 4 million Filipinos had DM in 2015, with more than 51 million diabetes-related deaths².

There are 2 types of diabetes: type 1 (T1DM) and type 2 diabetes mellitus (T2DM). Between the two types, T2DM is more prevalent, accounting for 90% of all DM cases worldwide⁴. T2DM results when the body becomes insulin resistant or when the insulin is insufficient to maintain a normal glucose level. Individual characteristics, genetics, and sedentary lifestyle (e.g., being obese [body mass index (BMI) ≥ 30 kg/m²], having a strong family history of T2DM, and having polycystic ovary syndrome) are factors associated with T2DM. Symptoms may be less evident in T2DM, and the disease is only diagnosed several years after its onset, when microvascular complications specifically affecting the eyes, kidneys, and nerves or macrovascular complications pertaining to cardiovascular and peripheral disease are already present⁴.

Once symptomatic, T2DM patients will present with polyuria, polyphagia, and polydipsia. Ketoacidosis is less common in T2DM, but is a common complication of T1DM, which is why the C-peptide level is used to distinguish between T1DM AND T2DM. C-peptide is usually at normal to elevated levels in T2DM patients, while it is suppressed in T1DM patients⁵.

1.2.2. Chronic kidney disease in patients with type 2 diabetes mellitus

One of the life-threatening complications of diabetes is chronic kidney disease (CKD). In a traditional definition, CKD is a progressive increase in proteinuria followed by declining kidney function that leads to end-stage renal disease (ESRD)^{1,6}. Globally, CKD is defined as a decrease in kidney function in the estimated glomerular filtration rate (eGFR) to less than 60 mL/minute/1.73 m² for at least 3 months, or presence of kidney damage (e.g., albuminuria)^{1,7}.

Hyperglycemia in patients with untreated DM is associated with elevated blood pressure, which in turn affects the kidneys by weakening the integrity of the glomeruli. This process causes protein to leak into the urine, and, eventually, these proteins could link together and trigger a scarring process. This scarring process worsens over time and eventually results to CKD.

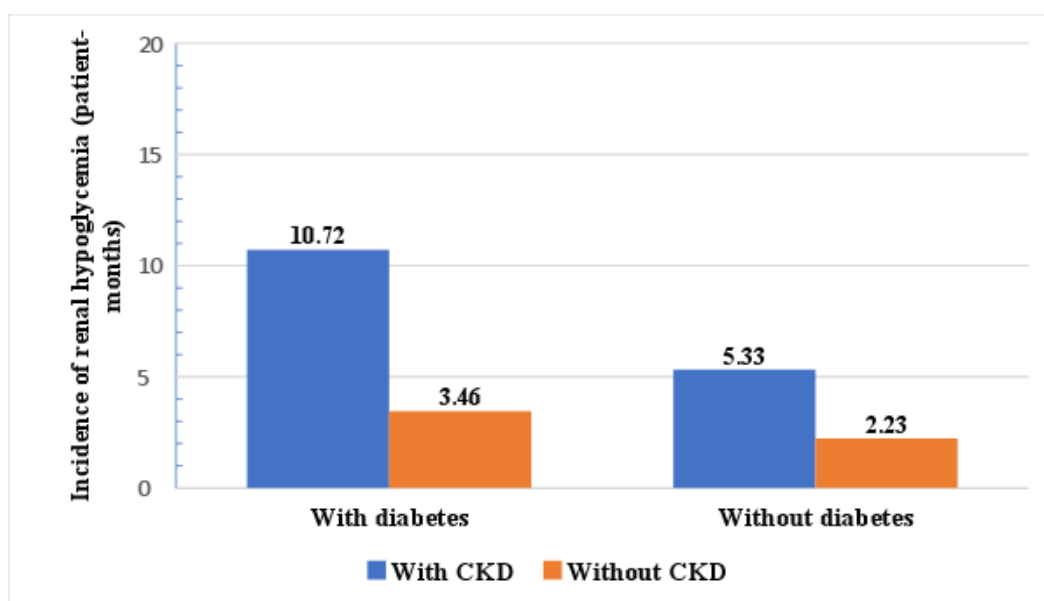
CKD in patients with T2DM is often asymptomatic and, often, diagnosis is already late and the condition has progressed into the advance stage^{4,8}. Patients with T2DM comprise 45% of those who are with CKD and undergo dialysis^{1,9}. Early signs of CKD in patients with T2DM are an increased excretion of albumin in the urine, weight gain, ankle swelling, nocturia, and hypertension. As the kidneys progressively fail, late signs include a rise in the blood urea nitrogen (BUN) and serum creatinine levels, nausea, vomiting, anorexia, weakness,

increasing fatigue, itching, muscle cramps especially in the legs, anemia, and less need for insulin¹⁰.

Generally, a person with diabetes is susceptible to nephropathy whether they use insulin or not; the risk is correlated to the length of time the person has diabetes¹¹. Renal hypoglycemia would then be an important parameter to strengthen the link between diabetes and renal failure. According to Dr. Romina Danguilan, a nephrologist from the National Kidney and Transplant Institute, CKD patients are very prone to hypoglycemia since they have lower appetite, they suffer from gastrointestinal complications, and their endogenous insulin are higher due to not being able to effectively clear insulin out of their system¹². Moen et al. studied renal hypoglycemia incidences and found that among patients with diabetes, the rate was 10.72 versus 5.33 per 100 patient-months for CKD versus no CKD, respectively; this comparison among patients without diabetes was 3.46 versus 2.23 per 100 patient-months (Figure 1)¹³.

In 2011, diabetes was the primary cause of new cases of ESRD in approximately 60% of patients in Malaysia, Mexico, and Singapore and in more than 40% of patients in the Republic of Korea, Hong Kong, the Philippines, Japan, the United States, and New Zealand^{11,14,15}.

Luk et al. in 2015 estimated that 35.93% of T2DM patients have CKD¹⁶. Per 100 individuals with T2DM, 41 develop ESRD¹⁷. Other studies demonstrated that among T2DM patients, 15% to 23% have moderate to severe CKD¹⁸. At the time of this writing, no specific data was available for Philippines.



CKD=chronic kidney disease; T2DM=type 2 diabetes mellitus

Source: Moen M, Zhan M, Hsu V, Walker L, Einhorn L, Seliger S, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol* 2009;4:1121-1127. Available from: <https://doi.org/10.2215/CJN.00800209>

As a complication itself, CKD is a risk for hypoglycemia, with or without diabetes. The excessive mortality associated with hypoglycemia makes this complication a significant threat to patient safety¹⁹. Prompt diagnosis and treatment for these patients shall then consider all the risks involved to provide the maximum health outcomes desired.

1.2.3. Screening and diagnosis of T2DM and CKD

For diagnosing DM, according to international guidelines, the standard tests are fasting blood sugar (FBS), random blood sugar (RBS), oral glucose tolerance test (OGTT) 2 hours post-prandial, glycated hemoglobin (HbA1c), capillary blood glucose (CBG), and fructosamine. Table 1 provides information on diagnosis of diabetes according to the previously mentioned

Figure 1. Incidence of renal hypoglycemia in T2DM patients with or without CKD

parameters.

Table 1. Parameters/diagnostic tests defining diabetes mellitus

Diabetes mellitus categorization	FBS (mmol/L)	RBS (mmol/L)	OGTT (mmol/L)
Normal	<5.6	<7.7	<7.7
Prediabetes with IFG	5.6 to 6.9	<7.7	<7.7
Prediabetes with IGT	<5.6	7.7 to 11	7.7 to 11
Diabetes mellitus	≥7.0	>11	>11

FBS=fasting blood sugar; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; OGTT=oral glucose tolerance test; RBS=random blood glucose.

Source: UNITE for Diabetes Philippines. Philippine Practice Guidelines on the Diagnosis and Management of Diabetes Mellitus. *Compendium of Philippine Medicine* 2014:16.

Patients with FBS levels of <5.6 mmol/L, OGTT 2-hours post-prandial <7.7 mmol/L, and RBS <7.7 mmol/L are considered normal (i.e., without diabetes). Patients with FBS levels of 5.6 to 6.9 mmol/L and normal OGTT and RBS levels are categorized as patients with prediabetes with impaired fasting glucose (IFG). Patients with OGTT and RBS level of 7.7 to 11 mmol/L and normal FBS levels are categorized as patients with prediabetes with impaired glucose tolerance (IGT). To be diagnosed as diabetic, a patient should have an FBS level of ≥7.0 mmol/L or either an OGTT or RBS levels of >11 mmol/L²⁰. For those who are asymptomatic, any 2 positive tests clinch the diagnosis; for those who are symptomatic, a single positive result is sufficient for a diagnosis of diabetes.

Screening for CKD is recommended after the initial diagnosis of T2DM and is done annually afterwards. CKD diagnostic tests include measurements of urinary albumin-creatinine ratio (UACR), serum creatinine, and eGFR calculation. In most patients with diabetes, CKD is attributable to diabetes if macroalbuminuria is present, which is defined as a UACR >300 mg/g per day. According to the Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, CKD defined by kidney damage for at least 3 months may be manifested either through pathological abnormalities, abnormalities in the composition of blood or urine (i.e., proteinuria), or abnormalities in imaging tests. Moreover, regardless of kidney damage, a glomerular filtration rate (GFR) <60 mL/min/1.73 m² for at least 3 months is also indicative of CKD²¹.

Stages in the development of CKD, as identified by the KDOQI guidelines²², are defined by the eGFR (Table 2). The calculation of eGFR is done through the use of different formulae (i.e., Cockcroft-Gault [CG], Modification of Diet in Renal Disease study, and Chronic Kidney Disease-Epidemiology Collaboration) using the serum creatinine values. In the Philippines, calculation is done using the CG formula.

Table 2. Stages of CKD according to KDOQI classification

Stage	Description	Renal function (eGFR) (mL/min/1.73 m ²)
1	Kidney damage with normal GFR	≥90
2	Kidney damage with mild GFR	60 to 89
3A	Mild to moderate GFR	45 to 59
3B	Moderate to severe GFR	30 to 44
4	Severe GFR	15 to 29
5	Kidney Failure	<15 or dialysis

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; KDOQI=Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Source: The Renal Association. *CKD Stages*. Available from: <https://renal.org/information-resources/the-uk-eckd-guide/ckd-stages/>.

Progression of kidney dysfunction is defined as an accelerated progression of CKD manifested by a sustained decrease in eGFR by at least 25% and a change in eGFR category within 12 months, or a sustained decrease in eGFR by 15 mL/min/1.73 m² per year. Patients with such sustained decrease have higher risk of progressing to ESRD²³.

1.3. Management and treatment of CKD-T2DM patients

Management of T2DM is initiated once diagnosis is confirmed. Initial treatment involves lifestyle modification; however, if blood sugar is deemed uncontrollable and exceeds the

control limit, practitioners may prescribe oral antidiabetic agents (OADs) or insulin, whichever is more appropriate²⁰.

The therapy depends on the results of diagnostic tests and laboratory examinations. If HbA1c is <9% or FBG is <250 mg/dL (<13.9 mmol/L), the patient may be started on a monotherapy or combination therapy, while patients with HbA1c ≥9% or FBG ≥250 mg/dL (≥13.9 mmol/L), the patient may be started on a combination therapy or an insulin therapy⁶. The degree of and risk for hypoglycemia, BMI, presence of comorbidities (e.g., renal, cardiovascular, and hepatic), preferences of and access to treatment, and compliance are also considered in determining the therapy for a particular patient. Other than that, agent characteristics, such as efficacy and durability of lowering blood glucose, risk of inducing hypoglycemia, effects on weight, contraindications, adverse effects, and costs and insurance coverage, are also taken into consideration⁶.

Treatment of T2DM patients with CKD, on the other hand, poses more challenges. For these patients, in addition to the above-mentioned criteria, kidney function and safety of the drug are also taken into consideration. For instance, insulin is generally safe for T2DM patients regardless of the stage of CKD. On the other hand, metformin is safe for patients with CKD 1 or 2; however, it should be used with caution for patients with CKD 3 and is not safe for patients with CKD 4, and 5 or ESRD. Table 3 shows the different drugs used for T2DM and their applicability for different CKD stages²⁰. It can be noted that most dipeptidyl peptidase-4 (DPP4) inhibitors are safe for patients with CKD 1 to 4 but should be used with caution for patients with CKD 5 or ESRD. Meanwhile, the safety profile is different for different sulfonylureas (SUs).

Table 3. Treatment for T2DM patients with CKD according to CKD stages

Drug class	Medication	CKD 4	CKD 5 (ESRD)	CKD 5 + dialysis
		eGFR=15 to 29 ml/min	eGFR<15 ml/min	eGFR<15 ml/min
Insulin	NPH	No dose adjustment required on kidney function		
	Regular	No dose adjustment required on kidney function		
SU 2 nd generation	Gliclazide	Lower dose	Consider alternative agent	
	Glipizide	No dose adjustment required on kidney function		
	Glimepiride	Lower dose	Consider alternative agent	

Drug class	Medication	CKD 4	CKD 5 (ESRD)	CKD 5 + dialysis
		eGFR=15 to 29 ml/min	eGFR<15 ml/min	eGFR<15 ml/min
DPP4 inhibitor	Sitagliptin	Use lowest dose (25 mg daily)		Use with caution
	Saxagliptin	Lower dose to 2.5mg once daily (<50 ml/min)	Consider alternative agent	Use with caution
	Linagliptin	No dose adjustment required on kidney function		Use with caution
	Alogliptin	Use lowest dose (6.25 mg daily)		Use with caution

CKD=chronic kidney disease; ESRD=end-stage renal disease; DPP4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; NPH=neutral protamine Hagedorn; SGLT2=sodium-glucose co-transporter 2; SU=sulfonylurea; T2DM=type 2 diabetes mellitus; TZD=thiazolidinedione.

Source: Harper, W et al. Chronic Kidney Disease in Diabetes. Canadian Diabetes Association Clinical Practice Guidelines. *Canadian Journal of Diabetes*. 2013:S61-S68.

1.4. The need for a clinically and cost-effective and safe treatment in the Filipino context

Treatment of T2DM poses an important challenge in people with CKD, which is greatly influenced by the severity of kidney dysfunction. Determination of therapy used considers the adequacy of glycated hemoglobin, potential complications or adverse effects of oral antidiabetic therapies, and the varied responses to therapy as kidney dysfunction progresses^{18,24}. As a result, once an individual progress to late stages of CKD, treatment of diabetes is limited to only a few therapies. In terms of physician choice, the Philippine National Formulary (PNF) currently includes only insulin and SUs. Thus, there may be a case made to add a newer class of antidiabetic medication to the PNF, should they be deemed efficacious, safe, and cost-effective in the Filipino market conditions.

As mandated by Executive Order 49 series 1993, the PNF Volume 1 shall be used as a basis in the procurement and requisition of drugs and medicines by the government²⁵. Furthermore, according to the Implementing Rules and Regulations of the Republic Act 9502 or the “Universally Accessible Cheaper and Quality Medicines Act of 2008”, only drugs and medicines in the latest edition of the PNF can be procured by government agencies or reimbursed by the Philippine Health Insurance Corporation (PhilHealth)²⁶. Due to the limited resources, it is imperative to determine not only if a certain treatment is clinically effective and safe but also if it is cost-effective.

The most commonly used drugs for T2DM that are also listed in the PNF are listed in Table 4⁶. These drugs differ in their efficacy and safety profile as well as their route of administration, which in turn influence treatment compliance and preference.

Table 4. Drugs for treatment of T2DM listed in the PNF

Drug Class	Drug	Expected decrease in HbA1c	Hypoglycemia	Change in weight	Route of Administration
Insulin	NPH	0.9% to 1.1%	Yes (significant risk)	Weight gain	SC or IV
SU 2 nd Generation	Gliclazide	0.8%	Yes (minimal/mode rate risk)	Weight gain	PO

HbA1c=glycated hemoglobin; IV=intravenous; NPH=neutral protamine Hagedorn; PNF=Philippine National Formulary; PO=oral administration; SC=subcutaneous; SU=sulfonylurea; T2DM=type 2 diabetes mellitus.

Source: Harper, W et al. Pharmacologic Management of Type 2 Diabetes. Canadian Diabetes Association Clinical Practice Guidelines. *Canadian Journal of Diabetes*. 2013:S61-S68.

In the Philippines, local guidelines on the diagnosis, management, and monitoring of T2DM patients with CKD are not concretely defined. In a key informant interview done with Dr. Cecilia Jimeno, an endocrinologist and a member of the FEC, it was highlighted that, in practice, approximately 2 out of 3 T2DM patients are likely undiagnosed²⁷. Of those patients that are diagnosed, approximately 30% are expected to be treated with metformin monotherapy, while the rest are likely to receive a combination therapy of metformin and SU.

Upon diagnosis of CKD in these patients, the ones in the early stages (i.e., CKD 1, 2, and 3a) are expected to be treated either with SU or insulin, as per PNF; most likely, 70% of the diagnosed patients are treated with SU²⁷. Of these patients, 75% may progress to CKD 3b or 4 in 10 to 15 years²⁷.

On the other hand, among those who are diagnosed with CKD 3b, 4, or 5, the expectation was that approximately 33% are treated with SU, 33% are treated with insulin, and the remaining 33% are untreated mainly due to patient's refusal to treatment. These patients who are untreated are highly at risk of progressing to ESRD, which would require either dialysis or kidney transplant. Approximately 20% of T2DM patients with CKD 4 may progress to CKD 5, while 10% of all CKD 4 cases lead to death. Among the cases of T2DM with CKD 5, 8% of patients die due to renal dysfunction complications¹².

Further complicating the treatment, the behavioral self-management of CKD among T2DM patients is challenging due to the complex nature of the diabetes treatment^{28,29}. Health education alone has demonstrated to be not sufficient to promote and sustain healthy patient compliance with such an intensive treatment regimen³⁰. Self-management strategies of CKD

T2DM patients need to include multiple behaviors such as monitoring and treatment of glycemia, blood pressure, nutrition, smoking cessation, exercise, and medication adherence. In a study done in a tertiary hospital in the Philippines involving T2DM outpatients in 2013, approximately 83% of patients missed their medications at most thrice a week, while 16% missed their medications 4 to 6 times a week. Furthermore, less than 10% of the patients monitored their blood glucose daily over a week period. Compliance to lifestyle modification (i.e., following a healthful eating plan and performing at least 30 minutes of exercise) was also less than 10%³¹.

Patients with diabetes and chronic kidney disease can significantly reduce the chances of developing long-term complications by improving self-management activities^{32,33}. Despite this fact, treatment compliance of T2DM patients taking sitagliptin, gliclazide, and insulin varies globally from 33% to 59%^{34,35,44–49,36–43}. Through various studies, treatment compliance was assessed using survey questionnaire, electronic medical records, self-reports, pill count, and prescriptions refilling^{34,35,44–49,36–43}.

Compliance to therapy and treatment can be affected by many factors, which can be patient-related, therapy-related, or healthcare-system-related⁴⁹. Different studies have cited that adherence to treatment is influenced by complexity and nature of dosing regimen, safety and tolerability, and economic considerations^{50–53}. Major predictors of the poor treatment compliance include cost of medication, missed appointments, side effects of medication, psychological problems, treatment complexity, asymptomatic disease, inadequate follow up, poor patient provider relationship, patients' lack of insight in illness, patients' lack of belief in benefit of treatment, and barrier to access the healthcare facilities^{34,35,44–49,54,55,36–43}. Forgetfulness and pill burden are some of the most common reasons for medication non-adherence among type 2 diabetes patients^{34–39,42,44,46,49}.

This review seeks to evaluate the clinical efficacy, safety, and cost-effectiveness of sitagliptin in the treatment of patients with T2DM and CKD. In comparison with the drugs currently listed in the PNF (SUs and insulin), DPP4 inhibitors claim a relative HbA1c lowering efficacy of 0.7%, less episodes of hypoglycemic events (HGE), have a weight neutral effect, and are also orally administered, which, in turn, may lead to improved compliance compared to an injected treatment. With these in mind, the starting hypothesis to be verified in this study is that sitagliptin in T2DM patients with CKD 4 and 5 is non-inferior in efficacy to current drugs listed in the PNF, has a better safety profile, and an easier route of administration, which may lead to proving as a cost-effective intervention in T2DM patients with CKD 4 and 5. Results from this review will be used as evidence for the decision-making of whether sitagliptin should or should not be included in the PNF.

II. PRODUCT INFORMATION

2.1. Chapter Summary

- Insulin neutral protamine Hagedorn is commonly prescribed for T2DM with renal dysfunction. It can be administered subcutaneously or intravenously. Most common side effect is hypoglycemia; therefore, frequent monitoring of blood sugar levels is necessary to prevent symptomatic and severe hypoglycemic events.
- Gliclazide, which is first choice and first to be prescribed, and glipizide, which is the most representative of this drug class, are sulfonylureas. Both can be taken orally. This drug class may also cause hypoglycemia; therefore, frequent monitoring is needed during initiation of therapy but frequency of monitoring decreases when blood sugar levels are stabilized at a certain dose.
- Sitagliptin is from the dipeptidyl-peptidase 4 inhibitor class and is administered orally. Due to the inability of the kidneys to completely excrete the drug, dose reduction is recommended for CKD 4 and 5. Sitagliptin may also cause hypoglycemia but only on rare occasions.
- Severe hypoglycemic events can cause temporary to permanent neurological complication to an affected patient. Hypoglycemic events can be prevented by frequent monitoring of blood sugar levels and medication dose adjustment.

2.2. Comparative description

Comparison of the mechanism of action, dosage and route of administration, contraindications, adverse effects, and drug indications of insulin neutral protamine Hagedorn (NPH), sulfonylurea, and sitagliptin is summarized on Table 5. Use of these treatments in T2DM patients with CKD is also enumerated and discussed.

Table 5. Comparison of NPH insulin, sulfonylurea, and sitagliptin

Criteria	NPH Insulin	Sulfonylurea	Sitagliptin
Indicated in T2DM CKD patients	Yes	Glipizide: yes Gliclazide: partially; CKD 3-4	Yes
Mechanism of action	Regulates metabolism by receptor activation	Stimulates insulin secretion by receptor binding and channel inhibition	Inhibits DPP4 enzyme
Dosage	Dependent on patient requirement	Glipizide: 2.5 to 5 mg Gliclazide: 30 to 80 mg	25 to 100 mg

Criteria	NPH Insulin	Sulfonylurea	Sitagliptin
Route of administration	SC	PO	PO
Contraindications	Hyperglycemic coma and episodes of hypoglycemia	Hypersensitivity, diabetic coma, T1DM	Diabetic ketoacidosis
Adverse effects	Peripheral edema, pruritus, hypoglycemia, hypokalemia, weight gain, hypersensitivity reaction, immunogenicity	Hypoglycemia, increased serum creatinine and BUN	Hypoglycemia, increased serum creatinine
Drug interactions	Other ADAs, hypoglycemia-associated agents, etc.	Other ADAs, hypoglycemia-associated agents, etc.	Sulfonylurea and insulin
Implications in T2DM patients with CKD	CKD significantly reduces insulin clearance; hemodialysis increases insulin sensitivity and insulin clearance; peritoneal dialysis decreases insulin resistance.	Inconsistent recommendations regarding dose adjustments for CKD patients; limited information for ESRD patients; contrasting results from studies	Dose reduction recommended for moderate-to-severe CKD and ESRD; partially cleared by hemodialysis.
Treatment compliance	33.0% to 58.3%	40.2% to 56.5%	55.0% to 59.1%

ADA=antidiabetic agent; BUN=blood urea nitrogen, DPP4=dipeptidyl peptidase-4; NPH=neutral protamine Hagedorn; PO=orally administered; SC=subcutaneous.

2.2.1. NPH Insulin

NPH insulin is an intermediate-acting insulin formulation with a slower onset and longer duration of activity⁵⁶. It is indicated for treatment of patients with DM for the control of hyperglycemia⁵⁶.

2.2.1.1. Mechanism of action

Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrates, proteins, and fats. These target tissues include hepatic, skeletal, muscular, and adipose tissues⁵⁶.

2.2.1.2. Dosage and route of administration

The dosage determined based on the individual requirements of a patient. Insulin can be subcutaneously administered once or twice daily⁵⁶.

2.2.1.3. *Contraindications/special precautions*

NPH insulin is contraindicated to those who have hypersensitivity to any of its components, and to those who are having episodes of hypoglycemia. It should be used with caution in patients with hepatic and renal impairment⁵⁶.

2.2.1.4. *Adverse effects*

Adverse effects of NPH insulin include peripheral edema, pruritus, hypoglycemia, hypokalemia, weight gain, hypersensitivity reaction, immunogenicity, and hypertrophy and/or lipoatrophy at injection site⁵⁶.

2.2.1.5. *Drug interactions*

There are several listed drug interactions of NPH insulin. Certain drugs, when used with insulin, may enhance its hypoglycemic effect (e.g., other antidiabetic agents [ADAs], other hypoglycemia-associated agents, other blood glucose-lowering agents, DPP4 inhibitors, α -lipoic acid, guanethidine, herbs with hypoglycemic properties, androgens [except danazol], monoamine oxidase inhibitors, pegvisomant, prothionamide, quinolones, salicylates, selective serotonin reuptake inhibitors, β -blockers [except luvobunolol and metipranolol], edetate calcium disodium, edetate disodium, glucagon-like peptide [GLP]-1 agonists, liraglutide, metreleptin, pramlintide, and sodium-glucose linked transporter 2 [SLGT2] inhibitors). Use of insulin with hyperglycemia-associated agents and thiazide and thiazide-like diuretics may diminish its therapeutic effect. Lastly, use of pioglitazone may enhance the adverse/toxic effects of insulin, while use of insulin with rosiglitazone may enhance the adverse/toxic effects of the latter⁵⁶.

2.2.1.6. *Compliance to treatment*

Insulin is the most commonly prescribed ADA among CKD patients used in either monotherapy or combination therapy^{32,57}. The volume of insulin prescribed is 58.0 IU/day and the volume of insulin collected from pharmacies is 53.6 IU/day⁵⁸. Treatment compliance for insulin varies from 33% to 58.3%^{29,32,59,60}. Polypharmacy was found to be an important factor for non-compliance for CKD patients, as these patients take 4 to 6 different drugs for comorbid conditions associated with CKD^{57,60}. Other factors for non-compliance on insulin therapy includes forgetfulness, lack of information, complex dosing schedule, injection convenience and frequency, and financial capacity of the patients^{29,32,57,59,60}. Poorly compliant DM patients were prescribed with higher doses of insulin (66.4 IU/day) compared with those who are adherent (40.8 IU/day)²⁹. This could imply that physicians tend to increase the dose to compensate for poor compliance to improve the HbA1c levels.

2.2.1.7. *Use in T2DM patients with CKD*

CKD is associated with insulin resistance and, in advanced stages, decreased insulin degradation. Decreased degradation may lead to a notable decrease in insulin requirements or even the cessation of insulin therapy⁶¹.

The kidney is responsible for about 30% to 80% of insulin removal. Therefore, CKD significantly reduces insulin clearance. Regardless of the form of insulin chosen to treat diabetes, caution is still necessary for patients with CKD. Insulin-treated hospitalized patients require individualized care to ensure proper glycemic control⁹. Insulin levels in patients with diabetic nephropathy were higher than diabetic patients normal renal function⁶². In contrast to higher insulin levels, the metabolic response to regular insulin was generally lower in patients with diabetic nephropathy as in diabetic control patients^{62–64}. Furthermore, although patients with impaired kidney function have lower insulin requirements, no dose adjustment is required if the GFR is >50 mL/min^{59,65–67}.

An inpatient study randomizing weight-based basal and bolus insulin in patients with a GFR <45 mL/min/1.73 m² to 0.5 unit/kg body weight vs. 0.25 unit/kg body weight showed similar glycemic control but significantly less hypoglycemia in the group with the lower weight-based dose^{60,68}.

The highest self-reported incidence of HGE reported was due to insulin use. It was mentioned that hypoglycemia can have clinical implications on patient's quality of life⁶⁹. As the CKD of the patient progresses, the ability of the of the kidneys to clear insulin also decrease, which leads to accumulation of the insulin in the body thus causing hypoglycemia due to toxicity⁷⁰. A 1-year study by Mathioudakis et al. have identified 457 insulin-induced HGE from 385 patients, in which 63 and 66 insulin-induced HGE for type 2 DM patients with CKD 4 and 5, respectively. From the 457 insulin-induced HGE, there were 239 cases (52%) of mild hypoglycemia (60 to 69 mg/dL), 187 cases (41%) of moderate hypoglycemia (40 to 59 mg/dL), and 31 (7%) cases of severe hypoglycemia (<40 mg/dL)⁷¹.

Patients on hemodialysis or peritoneal dialysis pose an added challenge for insulin dosing. Hemodialysis improves insulin sensitivity but also increases insulin clearance, thus making it difficult to determine insulin requirements. Peritoneal dialysis, on the other hand, worsens insulin resistance. Exogenous basal insulin requirements were 25% lower on the day after hemodialysis compared with the day before, but insulin requirements before meals stayed the same⁷². In contrast, intraperitoneal administration of insulin during peritoneal dialysis provides a more physiologic effect than subcutaneous administration as this prevents fluctuations in blood glucose levels and insulin antibody formation⁷³. It is also important to take consideration

of higher insulin requirements due to insulin binding to the plastic surface of the dialysis fluid reservoir^{72,73}.

Patients with CKD 4 to 5 and those on dialysis have some degree of delayed gastric emptying. Because of this, therapy with oral ADAs may fail and end up on insulin therapy, as it is deemed more effective. This is because there is a lack of data concerning the use of oral ADAs in dialysis patients and their inability to adequately excrete many such agents. Moreover, patients on peritoneal dialysis obtain large amounts of calories from their dialysis fluid and often eat less than they might expect so that postprandial dosing may be helpful for them^{61,68,74}.

All available insulin preparations potentially can be used in CKD, while insulin analogues are generally preferred due to less risk for hypoglycemia. Insulin type, dose, and administration must be tailored to each individual patient in achieving euglycemia⁷⁵. For instance, insulin is preferred since it is useful to cover the glucose absorption that occurs with overnight peritoneal dialysis; however, it has less flexibility and restrictions in its ability to titrate insulin doses.

The starting dose may be lower in patients with CKD, since renal and hepatic metabolism of insulin is decreased in these patients. No dose adjustment is required if the GFR is at least 50 mL/min, while insulin dose should be reduced to approximately 75% of baseline if the GFR is between 10 and 50 mL/min and to 50% for a GFR of <10 mL/min, independent of the insulin type being used^{59,61,76}.

There is no inpatient insulin dose adjustment for CKD 1 and 2, decrease by 30%, 50%, and 60% insulin total daily dose for CKD 3, 4 and 5⁷⁷. As recommended by Snyder and Berns, if the GFR is 10 to 50 mL/min, the insulin dose should be reduced by 25%, and, if GFR is <10 mL/min, the insulin dose should be reduced to 50%. A patient on dialysis improves peripheral insulin resistance; therefore, that patient shall need less exogenous insulin⁷⁶. To define an insulin-induced hypoglycemia, the HGE should occur within the duration of action of the insulin, which varies depending on what type insulin was administered to the patient⁷¹.

2.2.2. Sulfonylureas

SUs stimulates insulin secretion from pancreatic β -cells, reduces insulin uptake and glucose output by the liver, and increases insulin sensitivity at peripheral target sites. Gliclazide is said to be the first choice and the first to be prescribed in this class, while glipizide is said to be the most representative for the drug class. Both drugs mentioned belong to 2nd generation SUs⁷⁸. Gliclazide is the only SU currently listed in PNF.

2.2.2.1. *Mechanism of action*

SUs, such as gliclazide and glipizide, act by binding to its receptor, which is a component of the adenosine-triphosphate-sensitive potassium channel in the pancreatic β -cells. Binding leads to the inhibition of these channels, resulting to calcium influx and subsequent stimulation of insulin secretion. The net effect is an increase in the responsiveness of pancreatic β -cells to both glucose and non-glucose secretagogues (e.g., amino acids). This net effect results to an increased release of insulin at all blood glucose concentrations⁷⁸.

2.2.2.2. *Dosage and route of administration*

2.29. SUs are orally administered. The recommended dose range may differ depending on the drug. Glipizide is administered at 2.5 mg daily dosage 30 minutes before breakfast; gliclazide, meanwhile, is administered at 30 to 80 mg daily dose. Dose adjustments may be required depending on blood glucose response, adverse reactions, and presence of renal or hepatic impairment⁷⁸.

2.2.2.3. *Contraindications/special precautions*

Contraindications to the use of SUs include hypersensitivity to the drug or any component of the formulation. Furthermore, SUs are contraindicated to patients who are unstable and/or with T1DM particularly juvenile DM, diabetic ketoacidosis, diabetic pre-coma and coma, serious infection, trauma, surgery, and severe renal or hepatic impairment. It is also contraindicated to pregnant and/or lactating patients⁷⁸.

2.2.2.4. *Adverse effects*

Different adverse effects are associated with the use of SUs. One notable effect is hypoglycemia. Other effects include cardiovascular, central nervous, dermatologic, endocrine and metabolic, gastrointestinal, genitourinary, neuromuscular and skeletal, ophthalmic, otic, and respiratory systems. It is also observed to increase serum creatinine and BUN⁷⁸.

2.2.2.5. *Drug interactions*

Certain drugs, when used with SUs, may enhance its hypoglycemic effect (e.g., other ADAs, other hypoglycemia-associated agents, DPP4 inhibitors, α -lipoic acid, androgens, β -blockers, cyclic antidepressants, fibric acid derivatives, GLP-1 agonists, guanethidine, metreleptin, oral miconazole, monoamine oxidase inhibitors, pegvisomant, posaconazole, prothionamide, quinolones, salicylates, selective serotonin reuptake inhibitors, SGLT2 inhibitors, sulfonamide antibiotics, thiazolidinedione [TZD], Vitamin K antagonists, and herbs with hypoglycemic properties). Other drugs may increase (e.g., ceritinib, cimetidine, clarithromycin, fluconazole,

ranitidine, oral miconazole, mifepristone, probenecid, and voriconazole) or decrease (e.g., colestesvelam, dabrafenib, enzalutamide, and rifampin) the serum concentration of SUs; other may increase (e.g., CYP2C9 inducers) or decrease (e.g., chloramphenicol and CYP2C9 inhibitors) its metabolism. SUs may also enhance the anticoagulant effect of Vitamin K antagonists⁷⁸.

2.2.2.6. Compliance to treatment

Among the SUs, glipizide, gliclazide, and glimepiride were found to be the most prescribed drugs for CKD patients^{55,57,79}. Methods such as pill counts, patient assessment, and prescriber interviews were used to assess the compliance^{54,79}. Compliance rate on SU therapy falls between 40.2% and 56.5%^{33,54,55,80}. Complex dosage schedule, forgetfulness, pill burden, treatment concerns such as hypoglycemia and weight gain, emotional stability, and lack of information were noted to affect the compliance of T2DM patients on SU therapy^{30,32,33,60}.

2.2.2.7. Use in T2DM patients with CKD

There are inconsistent recommendations regarding the required dose for gliclazide for T2DM patients with CKD. Hahr et al. concluded that gliclazide requires no dose adjustment for all stages of CKD⁶⁰; however, Arnouts et al. stated that, although no dose adjustments are needed, the drug must be started at low doses and titrated up every 1 to 4 weeks⁸¹. Dose adjustment should be carried out in steps of 30 mg, according to the blood glucose response. Each step should last for at least two weeks⁸².

However, according to the Canadian Diabetes Association 2013 Guidelines: Glycemic Management in T2DM by Dr. White, gliclazide will not require dose adjustments for CKD 1 to 3, reduced dose for CKD 4, and alternatives need not be considered for CKD 5 due to higher risk of hypoglycemia; unfortunately, data is limited for ESRD⁸³. The British National Formulary recommends gliclazide dose reduction in renal failure. This contrasts with several guidelines that recommend gliclazide as first choice SU and, therefore, requires further investigation^{84,85}.

Gliclazide causes less hypoglycemia than other SUs. In CKD 1, 2, and 3 (eGFR >30 mL/min), gliclazide can be used. There are no data in patients with severe CKD but, according to its metabolism, the use of gliclazide in reduced dose is also permitted in these subjects^{86,87}. Additionally, elderly patients above 60 years old, those with reduced liver or kidney function, and those who are fragile or malnourished are more likely to have low blood sugar when they take these medications⁸⁷. Evidence from the GUIDE Study, which assessed the risk of hypoglycemia associated with the treatment of modified-release gliclazide or glimepiride, revealed lower incidence of hypoglycemia in patients treated with gliclazide at a comparable level of diabetes control^{88,89}.

With the mechanism of action of this drug class involving insulin secretion, weight gain is expected due to increased levels of insulin. However, studies also show contrasting results. The study of Robb et al. in 1984 showed no overall significant change in body weight⁹⁰. More recent studies, particularly the study by Hissa et al. in 2015, showed that gliclazide has positive increase in weight⁹¹.

2.2.3. Sitagliptin

Sitagliptin is a DPP4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. At the time of launch, sitagliptin was a first-in-class agent. During the following 4 years, vildagliptin, saxagliptin, and linagliptin were also launched and were presented in the Filipino market. Since then, additional other 7 DPP4 agents have been commercialized around the world.

2.2.3.1. *Mechanism of action*

Sitagliptin inhibits DPP4 enzyme, which results in prolonged active incretin levels. Incretin hormones regulate glucose homeostasis by increasing the synthesis of insulin and its release from pancreatic β -cells. It also decreases glucagon secretion from pancreatic α -cells. Incretin hormones are rapidly inactivated by the DPP4 enzyme^{92,93}.

2.2.3.2. *Dosage and route of administration*

Sitagliptin is taken orally at 100 mg dose once daily^{92,93}. For those with renal impairment, the dose may vary. Patients with creatinine clearance (CrCl) of less than 30 mL/min or those with ESRD requiring dialysis, the dosage is reduced to 25 mg once daily; those with CrCl of at least 30 mL/min to less than 50 mL/min can be given a dosage of 50 mg once daily⁹².

2.2.3.3. *Contraindications/special precautions*

Sitagliptin is not intended for treatment of diabetic ketoacidosis. It should not also be used if there is a history of serious hypersensitivity to sitagliptin (e.g., anaphylaxis, angioedema, and exfoliative skin conditions such as Stevens-John syndrome)⁹².

Special precaution should be taken if sitagliptin will be given to patients with T1DM, history of angioedema, moderate and severe renal impairment, pregnant, or lactating⁹².

2.2.3.4. *Adverse effects*

Adverse effects of sitagliptin include hypoglycemia, which is observed in 1% of patients, and nasopharyngitis, which is observed in 5% of patients⁹². Other rare adverse effects (occurs <1%) include increased serum creatinine⁹².

2.2.3.5. *Drug interactions*

When sitagliptin is used in combination with sulfonylureas or insulin, there is an increased risk of hypoglycemia. Furthermore, certain drugs may enhance the hypoglycemic effect of sitagliptin (e.g., α -lipoic acid, androgens, guanethedine, hypoglycemia-associated agents, insulin monoamine oxidase inhibitors, pegvisomant, prothionamide, quinolones, salicylates, selective serotonin reuptake inhibitors, and SUs). Other drugs may increase (e.g., lumacaftor, P-glycoprotein/ABCB1 inhibitors, and ranozoline) or decrease (e.g., lumacaftor and P-glycoprotein/ABCB1 inducers) the serum concentration of sitagliptin. Lastly, thiazide and thiazide-like diuretics may diminish the therapeutic effect of the drug⁹².

2.2.3.6. *Compliance to treatment*

Various studies compared the compliance of patients taking sitagliptin with other DPP4 inhibitors (i.e., linagliptin and saxagliptin), as well as with SUs, as an adjunct medication to metformin. Compliance on sitagliptin among T2DM patients range from 55% to 59.1%^{55,60,94,95}. Various reasons on non-compliance focused on forgetfulness, pill burden, and high cost of medicine^{54,60,80}.

2.2.3.7. *Use in T2DM patients with CKD*

DPP4 inhibitors, in monotherapy, are not used as a first line therapy for the majority of T2DM patients, as metformin still remains the gold standard; however, it can be considered as monotherapy in patients who have contraindications to metformin, SUs, or TZDs⁹⁶. Sitagliptin is largely excreted in urine, with 70% to 80% of an oral dose appearing unchanged in the urine; thus, if used among ESRD patients, a dose reduction to 25 mg daily is recommended⁶¹. It also requires dose adjustment for patients with CKD, for instance, a reduction to 50 mg for moderate-to-severe renal insufficiency (GFR of 30 to 50 mL/min) may be recommended⁹⁶. Approximately 2- and 4-fold increase in plasma area-under-the-curve in T2DM patients with moderate renal insufficiency and in patients with severe renal insufficiency, including patients with ESRD on hemodialysis, respectively, were observed⁸¹. On the other hand, no dose adjustment is necessary due to an approximate non-clinical 1.1- to 1.6-fold increase in plasma area-under-the-curve of sitagliptin as observed in patients with mild renal insufficiency⁸¹. Furthermore, it may be given regardless of timing to the dialysis⁹⁶, although it is modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours post-dose)⁸¹. Sitagliptin is also effective when used in combination with metformin, TZDs, or SUs.

III. COMPARATIVE CLINICAL EFFICACY AND SAFETY OF NPH INSULIN, SULFONYLUREA, AND SITAGLIPTIN IN T2DM CKD PATIENTS

3.1. Chapter summary

- Systematic review included 4 randomized clinical trials, in which summary effect measures that are of main interest were HbA1c, adverse events, and hypoglycemic events, whereas 2 other summary effect measures were additional endpoints (i.e., FBS and clinically meaningful response).
- Overall, sitagliptin demonstrated non-inferior clinical efficacy to sulfonylurea, particularly in the change in HbA1c and FBS from baseline but has demonstrated statistically significant better safety profile in terms of less hypoglycemic events, making it an equally effective but safer alternative to the sulfonylurea. However, further information is still needed.
- No conclusion on comparative clinical benefit in terms of efficacy or safety can be drawn in comparison with insulin since there was no available data.
- All clinical trials presented were funded by a pharmaceutical company, thus posing a risk for bias. Also, there is a generally low risk for selection, performance, and detection bias and generally high attrition and reporting bias.

3.2. Methods

No direct head to head or observational studies were submitted by the applicant in the given population. As a result, the clinical efficacy and safety data of NPH insulin, SUs, and sitagliptin in T2DM patients with CKD 4 and 5 were reviewed based on published data from different randomized controlled trials. For the purpose of this review, glipizide was chosen to represent SUs due to the availability of data.

3.2.1. Research question and objectives

This review aims to assess the clinical efficacy and safety of sitagliptin compared with SU (as represented by glipizide) and insulin (as represented by NPH) for T2DM patients with CKD 4 and 5.

Specifically, it aims to assess and compare the change in HbA1c from baseline as the primary efficacy outcome. It also aims to assess and compare the incidence of AEs, SAEs, symptomatic HGEs, and severe HGEs as safety outcomes. Lastly, it aims to assess and compare the change in FBS from baseline and the proportion of clinically meaningful response as additional efficacy outcomes.

3.2.2. Eligibility criteria

Randomized clinical trials from peer-reviewed journals and clinical trials databases were included for the analysis. Trials should have included HbA1c, FBS, and proportion of clinically meaningful response as measures of clinical efficacy and incidence of adverse events (AEs) and symptomatic and severe HGEs as safety endpoints. These studies should have included male and female adult (≥ 19 years old) T2DM patients with CKD 4 and 5 (i.e., eGFR <45 mL/min/1.73 m²).

The exclusion criteria used were as follows:

- Review articles, prevalence studies, and other non-experimental studies
- Studies on T1DM patients
- Comparison of sitagliptin to drugs other than glipizide, DPP4, and insulin

3.2.3. Literature search

Articles on randomized clinical trials were searched in PubMed, HERDIN, ScienceDirect, EMBASE, and Google Scholar. Other data were obtained from clinicaltrials.gov. The search was done from September to October 2017. Keywords and MeSH terms used were “type 2 diabetes mellitus”, “chronic kidney disease”, “end-stage renal disease”, “renal insufficiency”, “sitagliptin”, “DPP4 inhibitor”, “sulfonylurea”, and “insulin”. Combinations of these keywords with Boolean operators were also used. Reference lists of studies and systematic reviews found were also searched. Related researches were considered.

3.2.4. Data collection process and data items

Full-text trials/journal articles were downloaded and read in soft and hard copy. These articles were searched for the following variables:

- a. Main author/s
- b. Year of publication
- c. Study design
- d. Study length
- e. Country
- f. Number of participants
- g. Patient characteristics

- h. Inclusion and exclusion criteria
- i. Treatment arms
- j. Continuation rate/discontinuation rationale
- k. HbA1c endpoint
- l. FBS endpoint
- m. Clinically meaningful response
- n. AEs
- o. Data on symptomatic and severe hypoglycemia
- p. Data on weight change
- q. Conclusion

3.2.5. Statistical analyses

There were 3 outcomes that were of main interest in this analysis; these are the HbA1c, AEs, and HGEs. The 2 other outcomes were additional endpoints (i.e., FBS and clinically meaningful response), since not all studies provided data for these.

The outcomes for clinical efficacy are HbA1c, FBS, and proportion of clinically meaningful response, while the outcomes for safety are AEs, hypoglycemia, and weight change. For the purpose of this review, clinically meaningful response is defined as reaching the target of less than 7% in HbA1c as a primary response and less than 6.5% in HbA1c as a secondary response.

The description of each effect measure is summarized in Table 6.

Table 6. Outcomes and corresponding reported effect measures for each endpoint

Outcome	Endpoint	Type of data	Reported effect measure
HbA1c	Efficacy	Continuous outcome (mean and mean difference)	Adjusted mean difference
FBS	Efficacy	Continuous outcome (mean and mean difference)	Adjusted mean difference
Clinically meaningful response	Efficacy	Dichotomous (proportion)	Frequency and proportion
AEs	Safety	Dichotomous (proportion)	Frequency and proportion (incidence)
HGEs	Safety	Dichotomous (proportion)	Frequency and proportion (incidence)

AE=adverse event; FBS=fasting blood sugar; HbA1c=glycated hemoglobin; HGE=hypoglycemic event.

Summary of the data reviewed and collected from the studies were presented in tables and discussed accordingly. Bias for each study was also assessed using the risk of bias assessment according to the Cochrane handbook⁹⁷. Meta-analysis was done only if at least 3 studies that were included.

3.3. Results and discussion

3.3.1. Study selection and characteristics

A diagram of the studies searched, screened, and included in the review is presented in Figure 2. Two hundred studies were initially found through the searches and were assessed for eligibility by their title and abstract. After removing duplicates, 106 studies were further evaluated. Of these, 63 studies were excluded through initial screening because the study designs used were not randomized clinical trials (i.e., 21 reviews, 8 editorial works, 6 case reports, 5 cohort studies, 5 retrospective studies, 4 in vivo studies, 4 systematic reviews, 3 cross sectional studies, 3 descriptive studies, 1 behavioral study, 1 commentary, 1 meta-analysis, and 1 observational study). The initial screening resulted to 43 studies initially included and for further evaluation. Of these, 40 were excluded during the final screening, because of not meeting the needed study parameters and criteria (i.e., 18 used different drug, 9 has different inclusion criteria, 5 reported different outcomes, 2 were post hoc analysis, 4 has no full text available, and 2 used a comparator that is not of interest). Finally, 3 studies were included in the final review. The characteristics of these studies are summarized in Table 7.

A multinational, randomized, double-blind, parallel-group trial done by Arjona Ferreira et al. in 2012⁹⁸ included 423 T2DM patients who were at least 30 years of age, and had moderate to severe renal impairment (<50 mL/min/1.73m²). Patients were randomized to either receive

sitagliptin 25 or 50 mg with matching placebo (n=211) or glipizide 2.5 to 20mg with matching placebo (n=212). The dosages of sitagliptin and glipizide are dependent on the renal function of the patient, glycemic control, and episodes of hypoglycemia. The outcomes that were measured were change from baseline in HbA1c and FBS for each treatment arm, clinically meaningful response, adverse events, and events of symptomatic and severe hypoglycemia.

The second published study included in the systematic review involved a multinational, randomized, double-blind, parallel-group trial done by Arjona Ferreira et al. in 2013⁹⁹ among T2DM patients at least 30 years of age, with ESRD, and on hemodialysis or peritoneal dialysis therapy for at least 6 months. This 54-week study included 129 patients, with 64 patients randomized to be given sitagliptin 25 or 50 mg with matching placebo and 65 randomized to be given glipizide 2.5 to 20mg with matching placebo. The dose of sitagliptin and glipizide are dependent on the renal function of the patient, glycemic control, and episodes of hypoglycemia. The outcomes that were measured were similar with the previously mentioned study of the same author. These 2 published studies included the NCTI as one of its study site.

The third study of Chan et al. in 2008¹⁰⁰ was a multinational, randomized, double-blind, parallel-group trial with a 12-week placebo phase and a 42-week continuation phase with active therapy. It included 91 patients of at least 18 years of age, 27 of which are Asian, and all have CKD 4 to 5. The drug of interest was sitagliptin with dosage at 50 or 25 mg, which are the doses recommended for CKD 4 and 5, respectively. The comparator was initially a matching placebo, which was later changed to glipizide with dosage at 5 to 20 mg. The outcomes that were measured and presented were change from baseline in HbA1c and FBS for each treatment arm, as well as adverse events and events of symptomatic hypoglycemia.

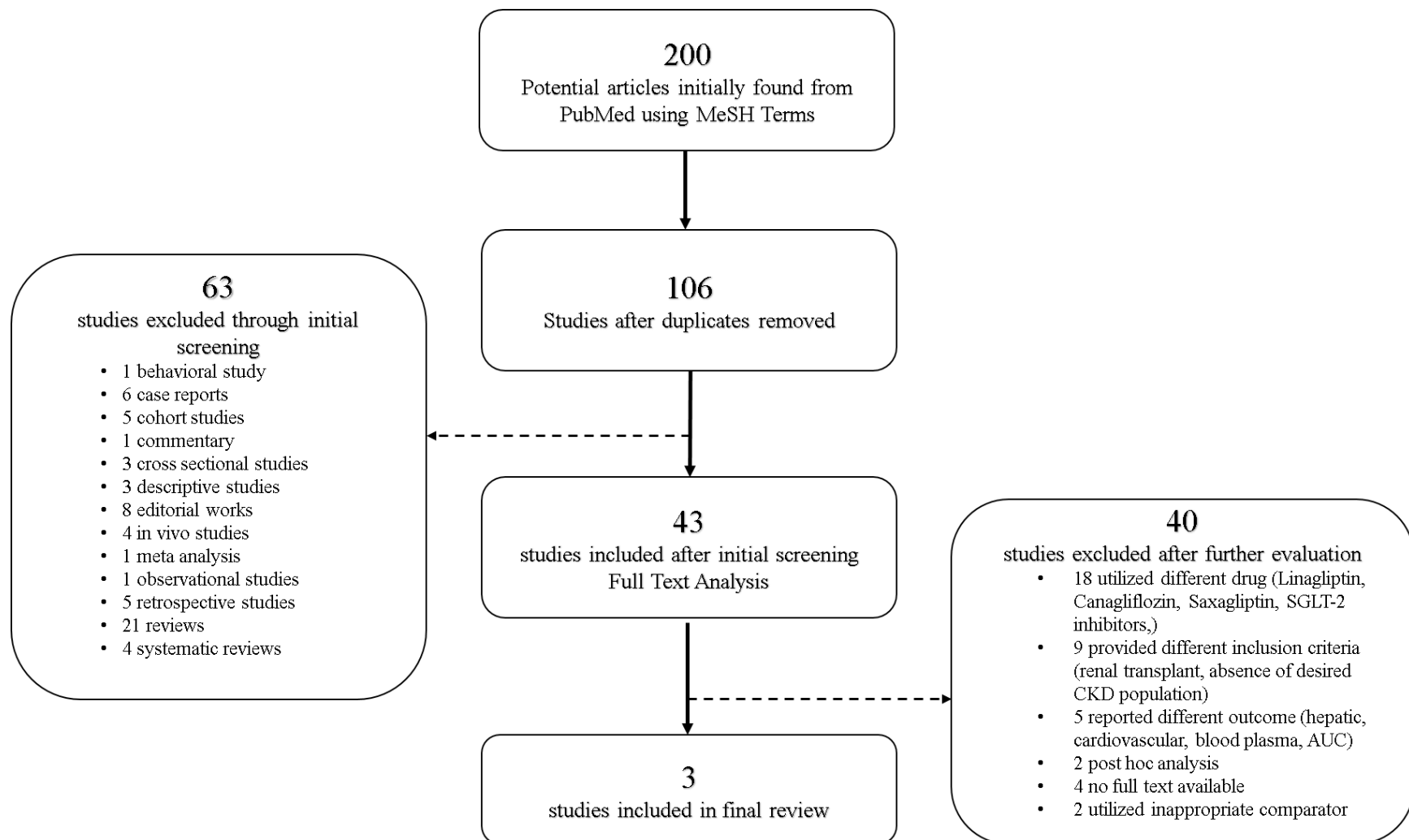


Figure 2. Flow diagram of literature search and screening

Table 7. Individual study characteristics

Main author	Year	Study design	Population characteristics		Sample Size	Treatment arms	Duration	Efficacy endpoints	Safety endpoints
Arjona Ferreira et al.	2012	Multinational, randomized, double-blind, parallel-arm study	Age	≥30 years or older	423	Sitagliptin 25 or 50mg or matching placebo (n=211) vs glipizide 2.5 to 20mg or matching placebo (n=212)	54 weeks	Change in HbA1c and FBS from baseline; clinically meaningful response	AEs, symptomatic and severe events of hypoglycemia
			Baseline HbA1c	7.0-9.0%					
			BMI	-					
			eGFR	Moderate to Severe: <50 ml/min/1.73m²					
Arjona Ferreira et al.	2013	Multinational, randomized, double-blind, parallel-arm study	Age	≥30 years or older	129	Sitagliptin 25 or 50mg or matching placebo (n=64) vs glipizide 2.5 to 20mg or matching placebo (n=65)	54 weeks	Change in HbA1c and FBS from baseline; clinically meaningful response	AEs, symptomatic and severe events of hypoglycemia
			Baseline HbA1c	7.0%-9.0%					
			BMI	-					
			eGFR	ESRD on HD/PD therapy for at least 6 months					
Chan et al.	2008	Multinational, randomized, double-blind, parallel-group trial with a 12-week placebo phase and a 42-week continuation phase with active therapy	Age	>18 years of age	91	Sitagliptin 25 or 50 mg vs matching placebo (n=65)	12 weeks (placebo phase)	Change in HbA1c and FBS from baseline	AEs, symptomatic events of hypoglycemia
			Baseline HbA1c	6.5% to 10.0% (not on OHAs); 7.5% to 10.0% (stable insulin monotherapy)		Sitagliptin 25 or 50 mg vs glipizide 5 to 20 mg (n=26)	42 weeks (continuation phase)		
			BMI	-					
			eGFR	Moderate 30 to < 50 ml/min and not on dialysis; Severe < 30 ml/min and not on dialysis or ESRD on dialysis.					

AE=adverse event; BMI=body mass index; eGFR=estimated glomerular filtration rate; FBS=fasting blood sugar; HbA1c=glycated hemoglobin; HD=hemodialysis; PD=peritoneal dialysis.

3.3.2. Results of individual studies

The results of the review of the individual studies are presented in Tables 8 to 13. Meta-analysis was not performed for the studies due to different study populations (moderate-to-severe renal impairment versus ESRD) and different comparators (placebo, glipizide, etc.). Nevertheless, results were carefully reviewed and evaluated.

3.3.2.1. *Sitagliptin versus glipizide*

2.75. Table 8 presents the change from baseline in HbA1c reported from each study. As shown, results from all of the 3 studies agree that patients who received sitagliptin had a significant reduction in HbA1c from baseline; however, this change is not significantly different from the glipizide group for the Arjona Ferreira et al. studies. Chan et al., 2008 did not report a difference between groups at the end of 54 weeks, and the main outcome of the study was the demonstration in reduction from baseline in HbA1c significantly higher in patients who received sitagliptin than those who received the placebo. Overall, it can be concluded that all 3 studies agree that sitagliptin is comparable or non-inferior to glipizide in efficacy, particularly in terms of change from baseline in HbA1c.

Table 8. Change from baseline in HbA1c per treatment group and difference between treatment groups

Study		Treatment arm	Change from baseline in HbA1c (%)
Arjona Ferreira et al., 2012		Sitagliptin (n=135)	-0.8 (-0.9, -0.6)
		Glipizide (n=142)	-0.6 (-0.8, -0.5)
		Difference between groups	-0.1 (-0.3, 0.1)
Arjona Ferreira et al., 2013		Sitagliptin (n=59)	-0.72 (-0.95, -0.48)
		Glipizide (n=62)	-0.87 (-1.11, -0.63)
		Difference between groups	0.15 (-0.18, 0.49)
Chan et al., 2008	12-week placebo phase	Sitagliptin (n=62)	-0.6 (-0.8, -0.4)
		Placebo (n=26)	-0.1 (-0.4, 0.2)
		Difference between groups	-0.5 (-0.8, -0.2)
	54-week placebo/glipizide	Sitagliptin (n=51)	-0.7 (-1.0, -0.4)
		Placebo/glipizide (n=25)	-0.8 (-1.2, -0.4)
		Difference between groups	-

HbA1c=glycated hemoglobin; n=number of patients per group.

Bold values represent significantly different change from baseline within and between groups.

– data is not available.

Table 9 shows the change from baseline in FBS reported in each study. As shown, results from all of the 3 studies agree that patients who received sitagliptin had a significant reduction in FBS from baseline; however, this change is not significantly different from the glipizide group for the Arjona Ferreira et al. studies. Similar to the previous discussion, Chan et al., 2008 did

not report a difference between groups at the end of 54 weeks; however, this study demonstrated that the reduction from baseline in FBS is significantly higher in the patients who received sitagliptin than those who received the placebo. Overall, it can be concluded that all 3 studies agree that sitagliptin is comparable or non-inferior to glipizide in efficacy, particularly in terms of change from baseline in FBS. This finding is similar with HbA1c.

Table 9. Change from baseline in FBS per treatment group and difference between treatment groups

Study		Treatment arm	Change from baseline in FBS (mg/dL)
Arjona Ferreira et al., 2012		Sitagliptin (n=136)	-17.5 (-24.5, -10.5)
		Glipizide (n=142)	-24.6 (-31.5, -17.8)
		Difference between groups	7.1(-1.9, 16.1)
Arjona Ferreira et al., 2013		Sitagliptin (n=59)	-26.6 (-38.0, -15.3)
		Glipizide (n=60)	-31.2 (-42.6, -19.9)
		Difference between groups	4.6 (-11.5, 20.7)
Chan et al., 2008 ^a	12-week placebo phase	Sitagliptin	-25.5 (-38.2, -12.8)
		Placebo	-3.0 (-15.7, 9.6)
		Difference between groups	-22.5 (-40.1, -4.9)
	54-week placebo/glipizide	Sitagliptin	-17.3 (-32.3, -2.2)
		Placebo/glipizide	-23.6 (-46.4, -0.7)
		Difference between groups	-

FBS=fasting blood sugar; n=number of patients per group.

^a sample sizes per group were not explicitly stated in the article

Bold values represent significantly different change from baseline within and between groups.

– data is not available.

Table 10 presents the proportion of patients in each study who showed clinically meaningful response. Due to the use of HbA1c as the indicator, which was established in some studies as not very accurate for an effect measure for this population, especially on ESRD, it may explain the inconclusiveness and variability of values obtained for the percentage of patients that achieved clinically meaningful response for glipizide and sitagliptin. Although statistical significance cannot be concluded based on these values, it can be seen that at most approximately half of the patients had clinically meaningful primary response. As expected, a smaller proportion reached the secondary response. Only the studies from Arjona Ferreira et al., 2012 and 2013 reported this outcome, though they also did not offer any rationale for the smaller proportion. There was no explanation for the lack of clinical meaningful secondary response in Chan et al. In the absence of this explanation, we can only hypothesize that patients were not followed as strictly, or compliance became an issue.

Table 10. Proportion of patients which showed clinically meaningful response

Study	Treatment arm	Primary response ^a (%)	Secondary response ^b (%)
Arjona Ferreira et al., 2012	Sitagliptin (n=135)	47.4	17.8
	Glipizide (n=142)	41.5	14.8
Arjona Ferreira et al., 2013	Sitagliptin (n=59)	43.5	29.0
	Glipizide (n=62)	55.9	30.5

^a reaching HbA1c <7% at the end of treatment period^b reaching HbA1c <6.5% at the end of treatment period

In terms of safety, Table 11 shows the proportion of patients who reported AEs for each study. In general, there is a smaller proportion of patients in sitagliptin who had AEs compared with glipizide. Furthermore, there are lesser patients who reported drug-related AEs and serious adverse events (SAEs). For studies by Arjona Ferreira et al. in 2012 and Chan et al. in 2008, there is a higher count of death among the patients in the sitagliptin group. Nevertheless, the deaths were not drug-related.

Table 11. Proportion of patients with adverse events reported

Study	Treatment arm	AEs n (%)	Drug- related AEs n (%)	SAEs n (%)	Drug- related SAEs n (%)	Death n (%)
Arjona Ferreira et al., 2012	Sitagliptin (n=210)	143 (68.1)	27 (12.9)	34 (16.2)	2 (1.0)	3 (1.4)
	Glipizide (n=212)	153 (72.2)	39 (18.4)	37 (17.5)	7 (3.3)	2 (0.9)
Arjona Ferreira et al., 2013	Sitagliptin (n=64)	53 (82.8)	10 (15.6)	23 (35.9)	0 (0.0)	4 (6.3)
	Glipizide (n=65)	52 (80.0)	13 (20.0)	21 (32.3)	0 (0.0)	6 (9.2)
Chan et al., 2008 ^a	Sitagliptin (n=65)	52 (80.0)	8 (12.3)	20 (30.8)	1 (1.5)	5 (7.7)
	Placebo/glipizide (n=26)	22 (84.6)	5 (19.2)	10 (38.5)	0 (0.0)	1 (3.8)

AE=adverse event; SAE=serious adverse event.

Note: Test for difference between proportions were not reported in the articles; however, the difference was tested by the authors of this dossier and no statistically significant difference based on a 95% confidence limit was found.

^a AEs reported were for the whole 54-week treatment period.

An important endpoint of interest for this evaluation is the incidence of HGEs (Table 12). In these studies, HGEs was defined as symptomatic and severe. Severe HGEs are those episodes that would require hospitalization and could be life-threatening.

In the study of Arjona Ferreira et al. in 2012 and the study of Chan et al. in 2008, there is a statistically significant lower number of patients with events of both symptomatic and severe HGEs in the sitagliptin group compared to the glipizide group. Only the study of Arjona Ferreira

et al. in 2013 reported that there is significantly lower number of patients with events of severe HGEs in the sitagliptin group compared to the glipizide group. Both this study and the study by Chan et al. showed that there were no events of severe HGEs in the sitagliptin group.

Table 12. Proportion of patients with reported events of symptomatic and severe hypoglycemia

Study	Treatment arm	Symptomatic hypoglycemia n (%)	Severe hypoglycemia n (%)
Arjona Fereira et al., 2012 ^a	Sitagliptin (n=210)	13 (6.2)	3 (1.4)
	Glipizide (n=212)	36 (17.0)	6 (2.8)
	Rate difference (95% CI)	-	-1.4 (-4.8 to 1.5)
Arjona Fereira et al., 2013 ^b	Sitagliptin (n=64)	4 (6.3)	0 (0.0)
	Glipizide (n=65)	7 (10.8)	5 (7.7)
	Rate difference (95% CI)	-4.5 (-15.3 to 5.6)	-7.8 (-17.1 to -1.9)
Chan et al., 2008 ^c	Sitagliptin (n=65)	3 (4.6)	0 (0.0)
	Placebo/glipizide (n=26)	6 (23.1)	-
	Rate difference (95% CI)	-18.5 (-37.7, -3.9)	-

CI=confidence interval.

^a Authors reported that the difference between the events of symptomatic hypoglycemia in the sitagliptin and glipizide is significantly different (p=0.001)

^b Authors reported that the difference between the events of symptomatic hypoglycemia in the sitagliptin and glipizide is not significantly different (p=0.3)

^c AEs reported were for the whole 54-week treatment period.

- data is not available

Based on clinical trial results described above, sitagliptin is non-inferior to glipizide in terms of efficacy, particularly in the change in HbA1c and FBS from baseline but has demonstrated statistically significant better safety profile in terms of less episodes of HGEs and other AEs, making it an equally effective but safer alternative to glipizide. The studies did not offer enough information to draw an informed conclusion on whether the improved hypoglycemic safety of sitagliptin would be reflected more in decrease of symptomatic rather than severe HGEs or vice versa.

3.3.2.2. *Insulin*

As for the clinical efficacy and safety of insulin represented by NPH, only one trial was retrieved that included renal insufficiency as its inclusion criteria. The study, conducted by University of Sao Paulo General Hospital in 2017¹⁰¹, implemented a randomized, cross-over, open label, active-controlled clinical trial with a 24-week duration each for first phase and second phase. This study includes 34 patients in Brazil aged 40 to 80 years including CKD stage 3 to 4. Drugs used in the trial were NPH insulin and insulin glargine. The outcomes that were measured and presented were change from baseline in HbA1c for each treatment arm, as well as adverse events such as capillary-determined hypoglycemia and severe hypoglycemia. As this study

was just recently completed, there are not yet any published results; the information presented here was based on details retrieved from clinicaltrials.gov.

3.3.3. Risk of bias

The risk of bias assessment was done according to the Cochrane Handbook¹⁰². Publication bias assessment and analysis was not performed since there is very few studies included. Risk of bias for each study are presented in Tables 14 to 17. Figure 3 summarizes this assessment.

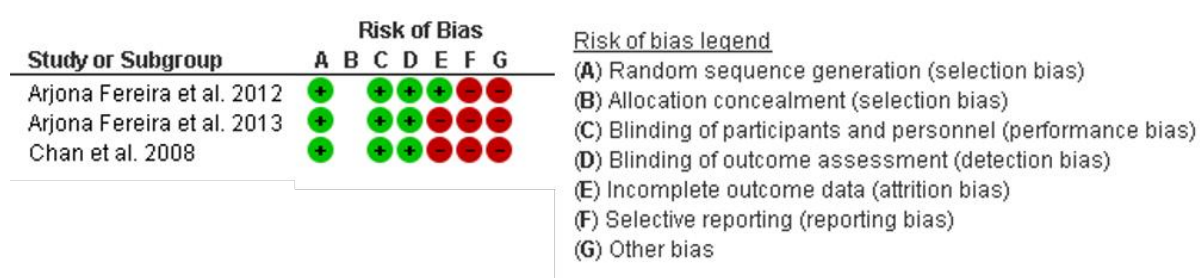


Figure 3. Summary of risk of bias assessment

+ denotes low risk; - denotes high risk; blank denotes unclear risk.

The study by Arjona Ferreira et al. in 2012 (has a high risk for other bias, since the study is sponsored by a pharmaceutical company. Also, there is a high risk for reporting bias, since not all outcomes were properly reported. Meanwhile, it has low risk for selection, performance, detection, and attrition bias since randomization and blinding were ensured through its design, and there is a low number of attrition.

Table 13) has a high risk for other bias, since the study is sponsored by a pharmaceutical company. Also, there is a high risk for reporting bias, since not all outcomes were properly reported. Meanwhile, it has low risk for selection, performance, detection, and attrition bias since randomization and blinding were ensured through its design, and there is a low number of attrition.

Table 13. Risk of bias assessment of the study by Arjona Ferreira et al., 2012

Type of bias		Reviewer's judgment	Support for judgment
Selection bias	Random sequence generation	Low Risk	The investigators used a computer-generated randomization schedule to receive sitagliptin or glipizide.
	Allocation concealment	Unclear risk	There was insufficient information to permit the

Type of bias		Reviewer's judgment	Support for judgment
			judgment for low risk or high risk
Performance bias	Blinding of participants and personnel	Low Risk	Blinding of participants and key study personnel were ensured, and unlikely that the blinding could have been broken. (double-blind study; sitagliptin and glipizide matching placebos were used to maintain blinding.)
Detection bias	Blinding of outcome assessment	Low Risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Attrition bias	Incomplete outcome data	Low Risk	Low number of attrition in the continuation phase is not enough to have a clinically relevant effect
Reporting bias	Selective reporting	High Risk	The article reported most pre-specified outcomes; however, some are not presented in proper tables, making it harder for readers to easily read the results.
Other bias	Other sources of bias	High risk	Study sponsored by a pharmaceutical company which markets the drug of interest.

Risk of bias assessment tool used was according to the Cochrane Handbook.

The risk of bias for the study of Arjona Ferreira et al. in 2013 (Table 14) is similar with the study in 2012; however, there could be a high risk for attrition bias since there is a high number of dropouts, which could be enough to have a clinically relevant effect.

Table 14. Risk of bias assessment of the study by Arjona Ferreira et al., 2013

Type of bias		Reviewer's judgment	Support for judgment
Selection bias	Random sequence generation	Low Risk	The investigators used a computer-generated randomization schedule to receive sitagliptin or glipizide.
	Allocation concealment	Unclear risk	There was insufficient information to permit the judgment for low risk or high risk

Type of bias		Reviewer's judgment	Support for judgment
Performance bias	Blinding of participants and personnel	Low Risk	Blinding of participants and key study personnel were ensured, and unlikely that the blinding could have been broken. (double-blind study) (Sitagliptin and glipizide matching placebos were used to maintain blinding.)
Detection bias	Blinding of outcome assessment	Low Risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Attrition bias	Incomplete outcome data	High Risk	High number of attrition in the continuation phase is enough to have a clinically relevant effect
Reporting bias	Selective reporting	Low Risk	The article reported all pre-specified outcomes and presented in proper tables, making it easier for readers to easily read the results.
Other bias	Other sources of bias	High risk	Study sponsored by a pharmaceutical company which markets the drug of interest.

Risk of bias assessment tool used was according to the Cochrane Handbook.

The risk of bias assessment for the study by Chan et al. in 2008 is shown in Table 15. Based on the judgment of the reviewers, there is high risk for attrition, reporting, and other bias. This is because there is a high number of attrition in the continuation phase, the imputation method used was the last-observation-carried-forward imputation, and the study is sponsored by a pharmaceutical company. Nevertheless, blinding and randomization was ensured by the design of the study, thus making it low risk for selection, performance, and detection bias.

Table 15. Risk of bias assessment of the study by Chan et al., 2008

Type of bias		Reviewer's judgment	Support for judgment
Selection bias	Random sequence generation	Low risk	Investigators used a computer-generated randomization schedule.
	Allocation concealment	Unclear risk	There was no mention of concealment of allocation of patients.
Performance bias	Blinding of participants and personnel	Low risk	The study has a double-blind design.
Detection bias	Blinding of outcome assessment	Low risk	The study has a double-blind design.
Attrition bias	Incomplete outcome data	High risk	High number of attrition in the continuation phase; LOCF was the imputation method used
Reporting bias	Selective reporting	High risk	The article reported all pre-specified outcomes; however, some are not presented in proper tables, making it harder for readers to easily read the results.
Other bias	Other sources of bias	High risk	Study sponsored by a pharmaceutical company which markets the drug of interest.

Risk of bias assessment tool used was according to the Cochrane Handbook.

3.4. Conclusion

This review found that, in all 3 studies, sitagliptin is non-inferior to glipizide in terms of efficacy in T2DM patients with CKD 4 and 5. Sitagliptin is expected to deliver better safety outcomes, including less episodes of HGEs, though there is only limited data suggesting statistically better safety profile with regards to lower risk of severe hypoglycemic events compared to glipizide in T2DM patients with CKD 4 and 5. However, caution should be taken in interpreting these results since there is a risk for bias, particularly in terms of attrition and reporting bias.

No conclusion on comparative clinical benefit in terms of efficacy or safety can be drawn in comparison with insulin since there was no available data.

IV.ECONOMIC VALUE

4.1. Chapter Summary

- Gliclazide and NPH insulin were chosen as comparators based on consultations with endocrinology and nephrology specialists.
- Sitagliptin can only be cost-effective based on the current threshold of 1 gross domestic product (GDP) per capita if there is a significant reduction in the current price.

4.2. Rationale for Assessment

This study evaluates the cost effectiveness of DPP4 inhibitors (marketed compound: sitagliptin) versus SU (marketed compound: gliclazide), and NPH insulin. Gliclazide and NPH insulin were chosen as comparators based on consultations with endocrinology and nephrology specialists^{12,27}. Incremental cost-effectiveness ratios (ICERs) between sitagliptin and its comparators, gliclazide and NPH insulin are estimated using Philippine data inputs. Results can inform listing of sitagliptin in the PNF as well as setting a reference price for procurement in public facilities.

4.3. Cost-effectiveness Analysis

4.3.1. Model Structure

A static Markov model constructed in a Microsoft Excel™ spreadsheet was constructed to compare costs and outcomes of drugs for diabetes: sitagliptin, gliclazide, and NPH insulin. The model consists of three health states: CKD 4 (eGFR of 15 to 29 mL/min/1.73 m²), CKD 5 (eGFR<15 mL/min/1.73 m²), and death. It assumes all patients are diagnosed with T2DM and can only progress from CKD 4 to 5 without reversal to the previous stage. A substate on the occurrence of severe HGE, which is described as one requiring hospitalization, is included in both CKD stages. The initial distribution of CKD patients among the stages were based on Philippine data reported by the CKD Clinic of the NKTi, ensuring that starting states are representative of the local prevalence. A schematic diagram of the model is presented in Figure 4.

The model has a cycle length of 1 year and utilised a time horizon of 7 years following the estimated life expectancy of patients in CKD 4 and 5. Patients included in the simulation are adults aged 60 years and above, which was based on the mean age of patients in clinical trials and demographic data of local CKD prevalence. A societal perspective was used in the cost-effectiveness analysis, wherein costs of treatment, management of severe hypoglycaemia, and patients' monitoring were included in the analysis. A government purchaser's perspective was used in the budget impact component; wherein only direct

treatment costs were considered. Costs and effects were discounted at 3.5% annually based on the recommendations of the Philippine Formulary Executive Council (FEC) and the National Economic and Development Authority (NEDA).

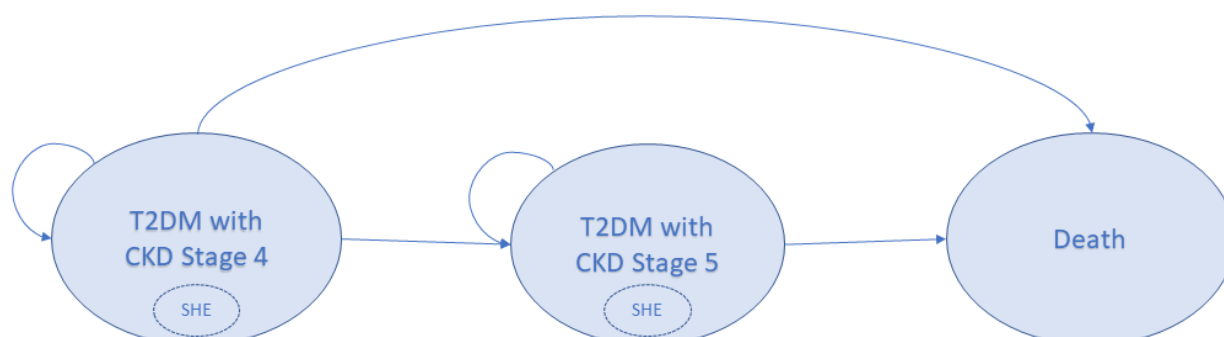


Figure 4. Markov Model Schematic Diagram

CKD=chronic kidney disease; SHE=severe hypoglycemic event; T2DM=type 2 diabetes mellitus.

4.3.2. Model Parameters

A systematic literature search was carried out to identify transition probabilities, measures of clinical effect, and health utilities. Details of each search conducted are outlined below.

4.3.2.1. Transition Probabilities

Probabilities of transitioning from CKD stages were derived from the NKTl CKD Clinic Report in 2014. Range of follow up were between three to fifteen months in the clinic. Probabilities were validated with a nephrology specialist based in the NKTl.

4.3.2.2. Clinical Effectiveness

Details of the systematic review conducted were presented in depth in the previous chapter. The review found that sitagliptin is non-inferior to glipizide in terms of efficacy in T2DM patients with CKD 4 and 5. However, sitagliptin is expected to deliver better safety outcomes, including less episodes of HGEs, which is the main measure of clinical effect used in the study. The evaluation assumes a class effect since there are no studies on the subgroup of interest using glimepiride, the drug more commonly used in the Philippines. Safety data on glipizide from the clinical trials is used as substitute.

4.3.2.3. *Outcomes*

The main outcome measure that was used in this study is the quality-adjusted life year (QALY). Health utilities per CKD severity were derived from a study by Neri et al. while disutility from an HGE were based on Harris et al.'s study on UK and US population. Because no local weights were available at the time of the study, utility values were no longer derived to Philippine values.

4.3.2.4. *Costs*

There were 4 main categories of costs included in the analysis: CKD maintenance cost (i.e., for dialysis and diabetes treatment), drug treatment cost, AE cost, and monitoring costs for T2DM. All inputs were reported in terms of annual cost per patient, based on assumptions and recommendations from key informants.

Drug costs used in the maintenance and treatment costs (for gliclazide and NPH insulin) were based on the Philippine Drug Price Reference Index (DPRI) (2016), with the addition of a 30% mark-up based on the recommendation of the FEC. As validated by an endocrinologist, the dose for insulin was assumed to not change regardless of kidney function. The components of the maintenance costs were also validated by an endocrinologist, and all drugs were assumed to be taken once daily for a year. Annual dialysis costs for CKD 5 patients were based on PhilHealth's latest publication of their case rate, assuming treatment is done thrice weekly for all patients with CKD 5. The cost of managing severe HGEs was also obtained from PhilHealth, with a 100% mark-up added as suggested by the FEC.

Estimating the monitoring cost per treatment arm required several assumptions and utilised various data sources. Each treatment arm had the same inputs, HbA1c testing and random blood sugar (RBS) testing; however, there were varied frequencies of RBS testing. Insulin had the highest treatment cost as RBS is assumed to be done thrice daily, compared to only once for gliclazide and sitagliptin. The cost of an HbA1c blood test was based on a nationally representative health facility survey conducted in 2016. The cost of supplies needed for home monitoring of RBS were obtained from a survey of suppliers in Bambang, Sta. Cruz, Manila, wherein the cheapest unit sale price was used.

Details of the cost data are in the Appendix.

All parameters in the model are summarised in Table 16.

Table 16. Summary of parameters

Parameters	Estimated value	Distribution	Reference
Baseline parameters			
Discount rate - outcomes	3.5%		Formulary Executive Council, NEDA
Discount rate - costs	3.5%		Formulary Executive Council, NEDA
USD exchange rate	51.29		Oanda, 6 November 2017
Transition probabilities (%)			
T2DM with CKD 4 to CKD 5	0.2857		NKTI CKD Clinic Report, 2014
T2DM with CKD 4 to CKD 4	0.4762		
T2DM with CKD 4 to death	0.2381		
T2DM with CKD 5 to CKD 5	0.9556		
T2DM with CKD 5 to death	0.0444		
Costs (Philippine Peso)			
Annual Maintenance Costs			
T2DM with CKD 4 (diabetes treatment)	4,474.54	Gamma	PhilHealth Case Rates, 2017
T2DM with CKD 5 (renal replacement therapy)	410,074.54	Gamma	PhilHealth Case Rates, 2017
Adverse event costs (per hospitalisation)			
Severe HGE	8,000	Gamma	PhilHealth Case Rates, 2017
Annual Drug Treatment Cost			
Sitagliptin	21,717.50	Gamma	Manufacturer submission
Gliclazide	1,712.95	Gamma	DOH Drug Price Reference Index 2016
NPH insulin	7,520.71	Gamma	DOH Drug Price Reference Index 2016
Annual Maintenance Cost			
Sitagliptin	6,755.40	Gamma	Facility and Supplier Survey
Gliclazide	6,755.40	Gamma	Facility and Supplier Survey
NPH insulin	12,566.20	Gamma	Facility and Supplier Survey

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Parameters	Estimated value	Distribution	Reference
Treatment Effects			
Severe hypoglycaemic event rate - sitagliptin	0.0135	Log-normal	Pooled trial data from Permsuwan, 2016
Severe hypoglycaemic event rate - gliclazide	0.0398	Log-normal	Pooled trial data from Permsuwan, 2016
Severe hypoglycaemic event rate – insulin	0.07	Log-normal	Matthioudakis, 2016
Utilities			
CKD 4	0.68	Log-normal	Neri et al., 2012
CKD 5	0.53	Log-normal	Neri et al., 2012
Disutility from a severe hypoglycaemic event	-0.0616	Log-normal	Harris et al., 2013

CKD=chronic kidney disease; DOH=Department of Health; HGE=hypoglycemic event NEDA=National Economic and Development Authority; NKTi=National Kidney and Transplant Institute; NPH=neutral protamine Hagedorn; T2DM=type 2 diabetes mellitus; USD=United States dollars.

4.4. Results

4.4.1. Base Case Analysis

While sitagliptin is non-inferior to gliclazide in terms of lowering HbA1c level, it has the lowest rate of severe HGE relative to gliclazide and insulin, thus, having the highest total QALYs. Sitagliptin is also the most expensive option out of the 3 drugs, with a price 3 times more expensive than insulin and over 12 times of the price of gliclazide. Even when monitoring costs are factored in, with insulin having the highest amount, the high unit price of sitagliptin makes the total treatment cost still the most expensive intervention. ICERs of sitagliptin are presented in Table 19 below.

The FEC currently has no explicit threshold used in past FEC appraisals. However, since 2 vaccine evaluations done by the Pharmaceutical Division, in collaboration with the Health Intervention and Technology Assessment Program (Thailand's health technology assessment [HTA] agency), used 1 GDP per capita in those analyses, the same threshold was applied (US\$ 2,950). When base case results are interpreted using this threshold, sitagliptin is not cost-effective versus either gliclazide or NPH insulin.

Table 17. ICERs of sitagliptin, gliclazide, and insulin

Intervention	QALYs	Costs (PHP)	ICER* (PHP)	ICER* (USD)
Sitagliptin	2,178.98	1,468,909,170.56		
Gliclazide	2,172.75	1,406,800,735.76	9,960,142.59	194,192.68
Insulin	2,165.59	1,444,253,382.76	1,840,522.60	35,884.63

* ICER vs sitagliptin

ICER=incremental cost-effectiveness ratio; NPH=neutral protamine Hagedorn; PHP=Philippine Peso; QALY=quality-adjusted life year; USD=United States Dollar.

4.4.2. Uncertainty Analysis

4.4.2.1. Methodological Uncertainty

To test for structural and methodological uncertainty, scenario analyses were conducted to test varying rates of discounts applied to sitagliptin, HGEs, and monitoring costs. This analysis shows how the ICER values increase or decrease when only one variable is changed. The analysis was

done on these variables as they are perceived to influence the results the most. Results are presented in Figure 5.

Increasing the rate of severe HGEs has the greatest effect of both ICERs for gliclazide and NPH insulin (over 100% change). Monitoring cost had the least effect on the ICERs, albeit still notable (8% to 17% change).

Extending the time horizon to 17 years and 5 years were also explored; however, this did not change the ICER. The same can be said for the discount rates on costs and outcomes used, which had no effect on the overall ratio.

4.4.2.2. *Parameter Uncertainty*

Given that the price of the sitagliptin is the largest determinant for cost effectiveness, a one-way scenario analysis was conducted using different costs for sitagliptin based on possible price discounts offers. A price reduction of at least 33% is needed to make sitagliptin cost-effective (versus NPH insulin) based on the threshold of 1 GDP per capita. A higher discount is needed when compared against gliclazide, as their monitoring costs are equal.

A probabilistic sensitivity analysis using Monte Carlo simulation of 10,000 iterations was carried out on all cost components and treatment effects. They were transformed into their probabilistic values based on their assumed distributions. These variables are considered as the main sources of uncertainty in the model. Costs were derived from various sources (e.g., DPRI and PhilHealth, with assumptions from expert opinion) while the treatment effect were based on single trial data.

Results of the simulation for sitagliptin versus gliclazide and insulin are presented in Figure 6A. Eighty-four percent of the trials versus gliclazide fell within the northeast quadrant of the cost-effectiveness plot, while the analysis against insulin yielded 62% in the same area (Figure 6B). The mean result is highlighted in pink in the figure and is shown in Table 18. The probabilistic ICERS showed higher values mainly due to the wider range of cost estimates used.

Table 18. Average costs, QALYs and ICER from the Monte Carlo Simulation

	Incremental QALY	Incremental Cost	ICER (PHP)	ICER (USD)
Sitagliptin vs Gliclazide	5.39	61,702,241.56	10,073,566.60	196,404.11

Health Technology Assessment: Sitagliptin for T2DM patients with CKD

Sitagliptin vs Insulin	12.77	24,469,292.83	2,058,566.67	40,135.83
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ICER=incremental cost-effectiveness ratio; PHP=Philippine Peso; QALY=quality-adjusted life year; USD=United States Dollar.

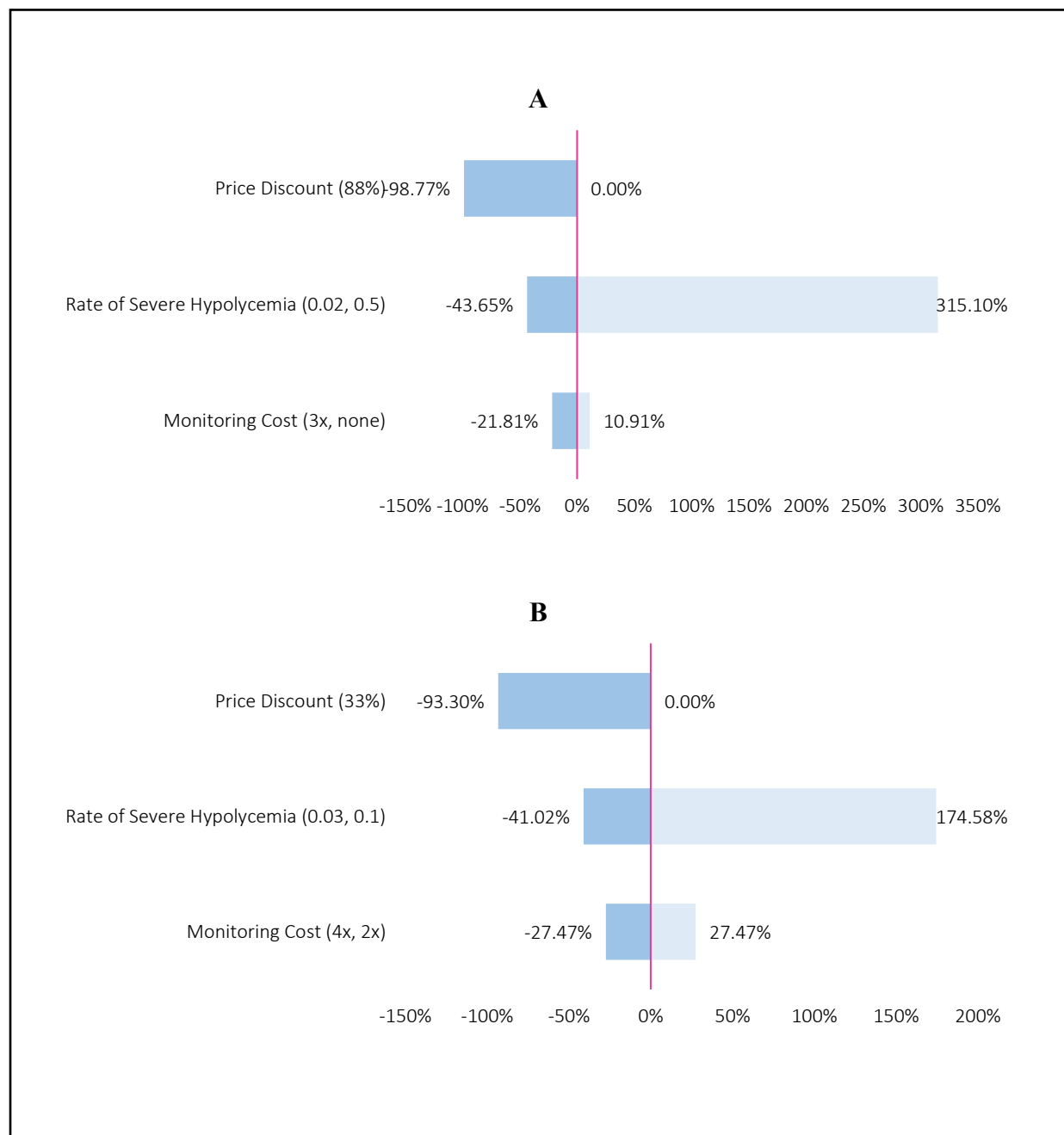
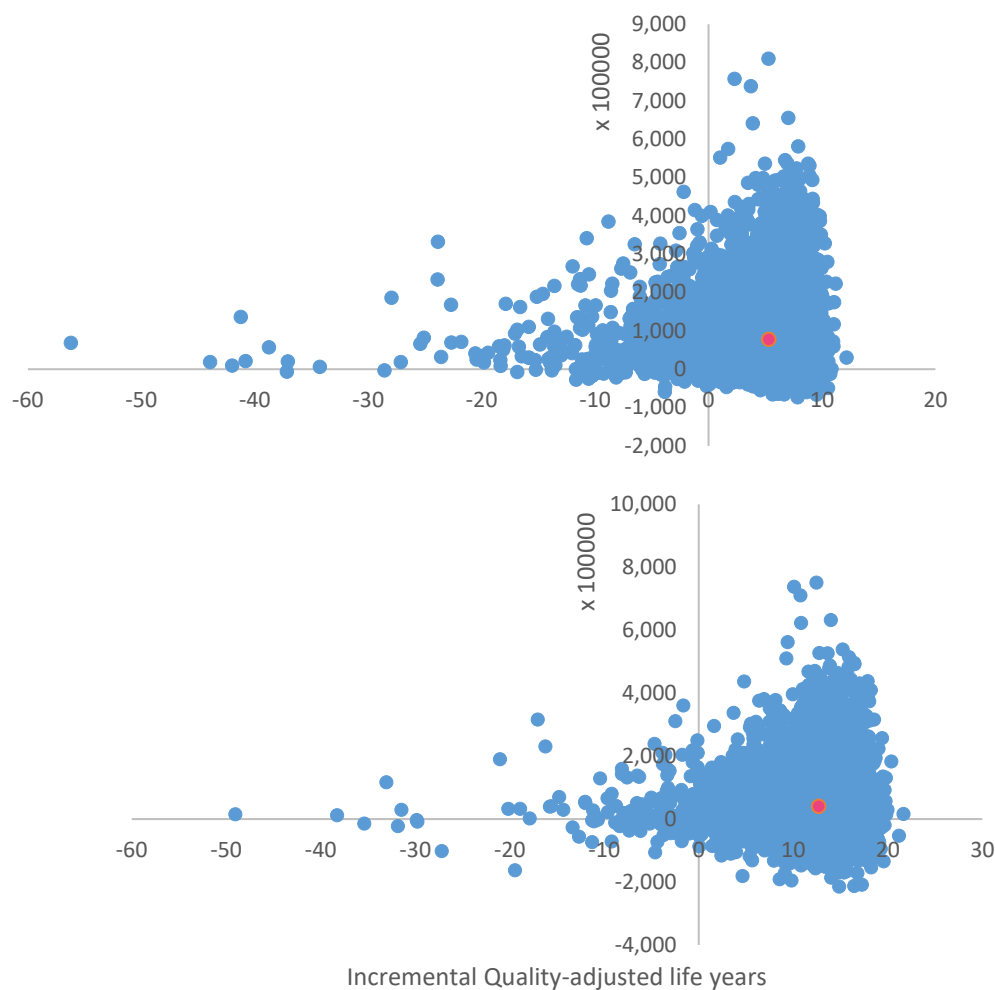


Figure 5. One-way scenario analyses: percent change in ICER (A) sitagliptin versus gliclazide (B) sitagliptin vs NPH insulin

ICER=incremental cost-effectiveness ratio; NPH=neutral protamine Hagedorn.



NPH=neutral protamine Hagedorn; QALY=quality-adjusted life year

Figure 6. Probabilistic sensitivity analysis for (A) sitagliptin versus gliclazide and (B) sitagliptin versus NPH insulin

4.4.3. Budget Impact Analysis

An additional analysis on budget impact based on existing prevalence data and assumptions on utilization was carried out to support the analysis. Based on the national prevalence of T2DM reported in the 7th National Nutrition Survey and a publication by Luk et al.¹⁶, the estimated number of diabetic CKD patients in the adult population of the Philippines is 1.44 million. This was further narrowed down to exclude those with eGFR rates above 30 or are in stages 1-3 of CKD.

Assuming only 30% will utilize, the estimated budget impact for one year for sitagliptin at varying price levels are presented in Table 19.

Table 19. Budget impact analysis of sitagliptin

	PHP	USD
Base Case (current price offer)	43,513,596.28	848,383.63
Discounted Price (88%) of Sitagliptin	5,221,631.55	101,806.04
Discounted Price (33%) of Sitagliptin	29,154,109.51	568,417.03

V. OPINION OF THE HTA STUDY GROUP

5.1. Limitations

The rationale for this assessment arose due to the pipeline of activities of the DOH Pharmaceutical Division, especially on the request to reconsider sitagliptin for inclusion in the PNF exclusively for the CKD population. Due to the limited treatments available for this subpopulation, this drug was considered for review as it may have a potential role as well as serve as an affordable treatment due to the small population included.

The assessment encountered some limitations of the study. First, the assessment heavily relied on the limited published clinical trials obtained from 4 databases where only English articles were considered. Furthermore, the 3 trials obtained, all of which were funded by pharmaceutical industries, used glipizide instead of gliclazide as the active comparator. This demonstrates the limited data that is available.

Second, as for the model, the main outcome used was in terms of severe HGEs, which was assumed to incur hospitalization costs based on PhilHealth, since the trials reported a non-significant HbA1c reduction. Researchers suggest exploration of other outcome measure, such as glycated albumin, which is a new and potentially better indicator of glycemic control, particularly in ESRD patients^{103,104}.

Third, the assessment also considered local cost estimates of treatment and monitoring costs from available databases, selected local stores in Bambang, Sta. Cruz, Manila, and government facilities (e.g., NKTi), which include most patients that would be highly affected upon the release of this review. Acquisition costs of sitagliptin compared to gliclazide is much larger, which would be challenging to show value for money due to the availability of generic versions of the latter. However, this would lead to pharmaceutical companies' decision to reduce drug price. Due to this limitation, the local cost estimates might not be representative of the actual cost.

Fourth, utility and disutility values were based on studies conducted in other countries, which mostly involved American and European populations. Without existing well-established studies in T2DM patients with CKD, the reviewers performed an extensive and exhaustive search and applied very conservative assumptions where information was limited.

Lastly, a major limitation of the review is excluding other comorbidities such as cardiovascular risks associated illnesses, as well as other complications associated with diabetes (infections,

retinopathy, neuropathy, etc.). Based on these limitations, the findings of our review must be interpreted with caution.

Given these limitations, the findings would remain the same due to the following reasons. First, the ICER value of sitagliptin compared to gliclazide and to NPH insulin was extremely beyond the implicit 1-GDP per capita threshold. Second, due to insignificance of HbA1c reduction, the QALY values were not significantly different. One-way sensitive analyses showed that the major drivers of the assessment were the safety profile of the drugs (i.e., severe hypoglycemic events) and the costs that these events incur. This is especially noted on drug cost that needs major price reduction.

5.2. Overall conclusion

While sitagliptin provides better safety outcomes in terms of reduced risk of severe hypoglycemia, this added value is not justified by the difference in price when compared to the benefits and costs of gliclazide and insulin. Based on the results of the economic evaluation, sitagliptin can only be cost-effective based on the current threshold of 1 gross domestic product (GDP) per capita if there is a significant reduction (33% or 88%) in the current price.

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VII. Appendix

Cost Inputs	Unit cost	Quantity	Total Cost	Assumption
<i>Maintenance Cost (CKD4)</i>				
Aspirin	1.56	365.00	569.40	once daily, DPRI price + 30% markup
Statin	1.39	365.00	507.72	once daily, DPRI price + 30% markup
ACEI/ARB	1.01	365.00	370.11	once daily, DPRI price + 30% markup
Antidepressant	8.29	365.00	3,027.31	once daily, DPRI price + 30% markup
Total			4,474.54	
<i>Maintenance Cost (CKD5: CKD4 + Dialysis)</i>				
Dialysis and CKD4 costs	2,600.00	156.00	410,074.54	dialysis 3x a week, PhilHealth rate
<i>Direct cost of acute events</i>				
Severe hypoglycemia	8,000.00	1.00	8,000.00	PhilHealth case rate + 100% markup
<i>Treatment Cost (annual)</i>				
Insulin	20.60	365.00	7,520.71	10 ml vial used for 40 days, syringe, DPRI price + markup
Gliclazide (30 mg)	4.69	365.00	1,712.95	once daily, DPRI price + 30% markup
Sitagliptin	59.50	365.00	21,717.50	once daily, SRP
<i>Treatment Monitoring Cost (for Insulin)</i>				
Frequency of monitoring	3.00			
HBA1C	700.00	4.00	2,800.00	Facility survey
Glucometer	900.00	1.00	900.00	Bambang price

Cost Inputs	Unit cost	Quantity	Total Cost	Assumption
Strips	7.36	1,095.00	8,059.20	Bambang price
Lancet	0.60	1,095.00	657.00	Bambang price
Lancing Device	150.00	1.00	150.00	Bambang price
Total			12,566.20	
<i>Treatment Monitoring Cost (for Gliclazide)</i>				
Frequency of monitoring	1.00			
HBA1C	700.00	4.00	2,800.00	Facility survey
Glucometer	900.00	1.00	900.00	Bambang price
Strips	7.36	365.00	2,686.40	Bambang price
Lancet	0.60	365.00	219.00	Bambang price
Lancing Device	150.00	1.00	150.00	Bambang price
Total			6,755.40	
<i>Treatment Monitoring Cost (for Sitagliptin)</i>				
HBA1C	700.00	4.00	2,800.00	Facility survey
Glucometer	900.00	1.00	900.00	Bambang price
Strips	7.36	365.00	2,686.40	Bambang price
Lancet	0.60	365.00	219.00	Bambang price
Lancing Device	150.00	1.00	150.00	Bambang price
Total			6,755.40	