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Diabetes Pharmacotherapy Clinic Guideline

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Ministry of health

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Introduction

Diabetes is a complex disease, a chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control.
The World Health Organization (WHO) has reported that Saudi Arabia ranks the second highest in the Middle East and is seventh in the world for the rate of diabetes. It is estimated that around 7 million of the population are diabetic and almost around 3 million have pre-diabetes. In fact, diabetes has approximately registered a ten-fold increase in the past three eras in Saudi Arabia (1).
Diabetes mellitus (DM) has been found to be related to high mortality, morbidity, and vascular complications, accompanied by poor general health and lower quality of life.
Significant evidence exists that supports a range of interventions to improve diabetes outcomes.
The general administration of pharmaceutical care developed this guideline. The purpose of this guideline to help the clinical pharmacists who run the diabetes clinics.

Aim and scope:
In collaboration with the physicians, nurses, nutritionists and health educators, the clinical pharmacist has a crystallized role in advising patients with diabetes through continuous follow-up and instructing patients about how to deal with doses of insulin and ant anti-hyperglycemic agents. Also, provides therapeutic services for the treatment of diabetes and health problems resulting from these disturbances.
This guideline will determine the responsibilities and roles of the clinical pharmacist in diabetes clinic to monitor, follow up, educate the diabetic patients.

Targeted population:
Diabetic patients with the following criteria (but not limited):

- Has a Polypharmacy medication.
- Newly injectable medication.
- With Uncontrolled diabetes (Hba1c > 9).
- Has another Chronic disease as HTN, asthma, epilepsy …. etc.
- With an Uncontrolled lipid profile.
- With poor medication adherence.
- Unawareness hypoglycemia.

Targeted end user:
Clinical Pharmacists.

Setup:
Ambulatory Diabetes Clinics

Methodology:
Development of Diabetes Pharmacotherapy Clinic Guideline completed by reviewing and adopting the international guidelines (2020 American Diabetes Association & 2013 Clinical Pharmacists in Outpatient Diabetes Care) and pharmacotherapy references, literature review, and the MOH formulary. Then the panel of experts in the field of clinical pharmacists reviewed it. Finally, the guideline was reviewed and amended by endocrinologist consultants.

Conflict of interest:

This guideline was developed based on valid scientific evidence, critical assessment of that evidence, and objective clinical judgment that relates the evidence to the needs of practitioners and patients. No financial relationships with pharmaceutical, medical device, and biotechnology companies.

Funding:
No fund was provided

Updating:

The first version of this guideline created in 2020. The guideline will be updated annually if any changes or updates released by international/national guidelines, pharmacotherapy references, or MOH formulary.

Evidence-grading system

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

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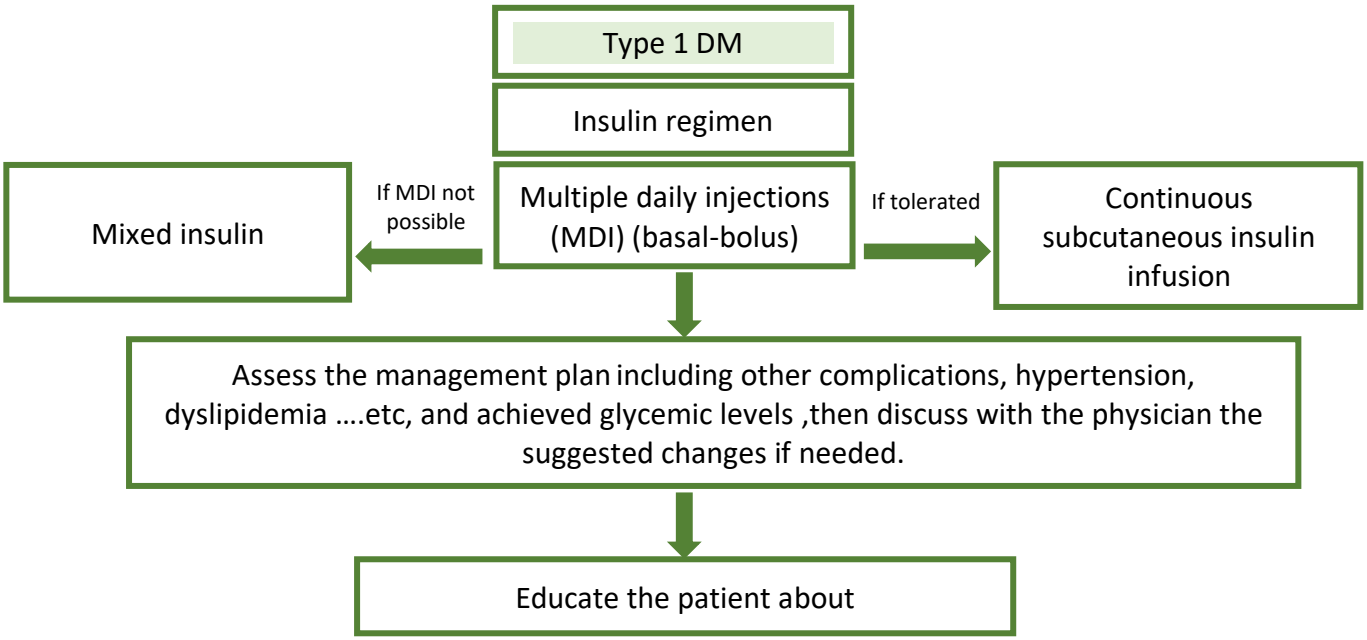
A. General Guidance [2]

Follow Up Pathway for Patients with Type 1 Diabetes Mellitus:



(1)

Management plan:

1- Type of insulin, doses, efficacy, duration and time of administration
2- The importance of life-style modification
3- Target glycemic levels
4- The impact of medication adherence in preventing the macro/micro-complication
5- Refer the patient to diabetic educator (for administration technique)

(2)

Self-monitoring blood glucose and insulin dose adjustment (table 1)

(3)

Insulin storage and stability

(4)

Managing the acute complication:

1- Hypoglycemia symptoms and management
2- Diabetic ketoacidosis/hyperglycemic hyperosmolar symptoms and management
3- Sick day meaning and how to manage the diabetes

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Follow Up Pathway for Patients with <u>Type 2 Diabetes Mellitus:</u>

Type 2 DM

Oral anti-hyperglycemia

- Monotherapy
- Dual therapy
- Triple therapy

Injectable anti-hyperglycemia

Insulin

Glucagon- like peptide

1) Assess the management plan and achieved levels then discuss with physician the changes if needed

2) Assess and Educate the patient about

1- Name of medications, doses, efficacy, and time of administration (with or without food) and related side effect (GI, risk of hypoglycemia...etc.)
2- The importance of life-style modification
3- Target levels
4- The impact of medications adherence in preventing the macro/micro-complication

Medications storage and stability

1- Type of insulin, doses, efficacy, duration and time of administration
2- The importance of life-style modification
3- Target levels
4- The impact of medication adherence in preventing the macro/micro-complication

Self-monitoring blood glucose and insulin dose adjustment (table 1)

Insulin storage and stability

1- Name of medications, doses, dose tapering, efficacy, time of administration and related side effect (GI, ...etc.)
2- The importance of life-style modification
3- Target levels
4- The impact of medication adherence in preventing the macro/micro-complication
5- Hyperglycemia Pregnancy complication.

Injection storage and stability

3) For all patients regardless of the type of medication

Managing the acute complication:
1- Hypoglycemia symptoms and management
2- Diabetic ketoacidosis symptoms and management
3- Hyperosmolar hyperglycemia symptoms and management
4- Symptoms of micro/macro complications.

Sick day meaning and how to manage the diabetes

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B. Management of Diabetes [3]

Diagnosis:

1. **Pre-diabetes:**

Criteria defining prediabetes*
• FBG 100 mg/dl (5.6 mmol/l) to 125mg /dl (6.9 mmol/l) (IFG)
• 2-h PG during 75 gm OGTT 140 mg/dl (7.8 mmol/l) to 199 mg /dl (11.0 mmol/l) (IFG).
• A1C 5.7-6.4% (39-47 mmol/mol)
FPG, fasting blood glucose; IFM, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose * For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher of the range.

2. **Diabetes can be diagnosed by one of four criteria:**
   1. Fasting plasma glucose ≥ 126 mg/dL (≥ 7.0 mmol/L);
   2. A 2-hour value from a 75-g oral glucose tolerance test (OGTT) ≥ 200 mg/dL (more than or equal to 11.1 mmol/L)
   3. Random plasma glucose level ≥ 200 mg/dL (≥ 11.1 mmol/L) with symptoms of diabetes
   4. Hemoglobin A_{1c} (HbA_{Ic}) ≥ 6.5% (≥ 0.065; ≥ 48 mmol/mol Hb).
   5. The diagnosis should be confirmed by repeating tests if clear hyperglycemia is not present.

Glycemic target for non-pregnant adult:

- HbA1c: less than 7 but more stringent A1C goals (6.5%) and Less stringent A1C goals (8%) could be as below criteria:

▪ Suggest more stringent A1C goals (6.5%) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy).

Patient criteria:

- ▪ With short duration of diabetes
- ▪ Type 2 diabetes treated with lifestyle or metformin only
- ▪ Long life expectancy
- ▪ No significant cardiovascular disease.

HbA1c	HbA1c	HbA1c
6.5 % **(C)**	Glycemic goal 7 % **(A)**	8 % **(B)**

Less stringent A1C goals (8%)

- ▪ With a history of severe hypoglycemia
- ▪ Limited life expectancy
- ▪ Advanced microvascular or macrovascular complications
- ▪ Extensive comorbid conditions
- ▪ Long-standing diabetes in whom the goal is difficult to achieve.

- Plasma glucose:

Pre-prandial capillary plasma glucose 80–130 mg/dL* (4.4–7.2 mmol/L).
Peak postprandial capillary plasma glucose <180 mg/dL* (10.0 mmol/L)

* More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

*Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes

Gestational diabetes- Glycemic target:

- Fasting 95 mg/dL (5.3 mmol/L) and either One-hour postprandial 140 mg/dL (7.8 mmol/L) or Two-hour postprandial 120 mg/dL (6.7 mmol/L).

C. Management Approach [4,5]

Pre-diabetes:

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI > or = 35kg/m^2, those-aged <60 years, and women with prior gestational diabetes mellitus. **(A)**

Type 1

- Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **(A)**
- Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **(A)**
- Intensive management using CSII and continuous glucose monitoring should be encouraged in selected patients when there is active patient/family participation

a- Initial insulin dose:

- These are initial doses only; they must be adjusted using Self-monitoring of Blood Glucose (SMBG) results. Patients may be particularly resistant to insulin if their blood glucose concentrations are high (glucose toxicity); once glucose concentrations begin to drop, insulin requirements often decrease precipitously. The weight used is the actual body weight.
- Insulin dose requirements can change dramatically with time depending on circumstances (e.g., a growth spurt, modest weight gain or loss, changes in physical activity, stress or illness).

Initial dose 0.3–0.5 units/kg
Honeymoon phase 0.2–0.5 units/kg
With ketosis, during illness, during growth 1.0–1.5 units/kg

1- Estimating Basal Insulin Requirements

- These are empiric doses only and should be adjusted using appropriate SMBG results (fasting or premeal).
- Basal requirements are approximately 50% of total daily insulin needs. Thus, basal insulin dose is approximately 50% of total daily dose (TDD).
- A conservative approach is to reduce the calculated 50% basal dose by 20% to avoid hypoglycemia

2- Estimating Premeal Insulin Requirements

- The premeal insulin requirements are approximately 50% of the TDD, usually divided equally into three doses initially, taken with each meal (i.e., breakfast, lunch and dinner), and then each premeal dose is individually adjusted based on blood glucose (BG) readings.
- The "500 rule" estimates the number of grams of carbohydrate that will be covered by 1 unit of rapid-acting insulin. The rule is modified to the "450 rule" if using regular insulin
- 500 or 450/TDD of insulin = number of grams covered.
- Supplemental doses of rapid-acting insulin are administered to acutely lower glucose concentrations that exceed the target glucose concentration. These doses must be individualized for each patient and again are based on the degree of sensitivity to insulin action. For example, if the premeal blood glucose target is 120 mg/dL and the patient's value is 190 mg/dL, additional units of rapid-acting insulin could be added to the premeal dose. The correction factor determines how far the blood glucose drops per unit of insulin given and is known as the "1,700 rule." For regular insulin, the rule is modified to the "1,500 rule".

3- Interpreting self-monitoring blood glucose concentration:

Test time	Effective dose of insulin	Target meal/snack
Pre-breakfast (fasting)	Pre-dinner/bedtime; intermediate/long acting insulin or basal insulin	Dinner or bedtime snack
Pre-lunch	Pre-breakfast regular/ rapid acting insulin	Breakfast or mid-morning snack
Pre-dinner	Pre-breakfast intermediate acting insulin or pre-lunch regular or rapid insulin	Lunch or mid-afternoon snack
Bedtime	Pre-dinner regular or rapid acting insulin	Dinner
2 hours postprandial	Premeal regular or rapid acting insulin	Preceding meal or snack
2-3 am or later	Pre-dinner intermediate acting insulin or basal if given at am	Dinner or bedtime snack

Table (1)

Type 2:

1. Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **(A)**
2. Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **(A)**
3. Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. **(A)**
4. The early introduction of insulin (0.1-0.2 unit/kg of long acting) should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. **(E)**
5. A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include cardiovascular comorbidities, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. **(E)**
6. Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor (Empagliflozin) or glucagon-like peptide 1 receptor agonist (Dulaglutide) with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors. **(A)**
7. In patients with type 2 diabetes who need greater glucose lowering than can be obtained with oral agents, glucagon-like peptide 1 receptor agonists are preferred to insulin when possible. **(B)**
8. Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. **(B)**
9. The medication regimen and medication-taking behavior should be re-evaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact the choice of treatment. **(E)**

Pharmacological Medications for DM:

Insulin:

1- Types of insulin:

Type of insulin:		Pediatric	Pregnancy
Rapid Acting	Lispro	≥ 3 years	B, starting to be used in pregnancy
	Aspart	≥ 2 years	B, starting to be used in pregnancy
	Glulisin	≥ 4 years	C
Short Acting	Regular	Limited data available for infants.	most studied, drug of choice in combination with NPH
Intermediate	NPH	Infants ≥ 6 months	drugs of choice
Long Acting	Glargine	≥ 6 years	C
	Detemir	≥ 2 years	B

Table (2)

2- Characteristics of U-100 (100units/mL) Insulins*:

Category	Drug name	Clarity	Onset	Administration rout	Administration time before meal (min)	Peak (hr)	Duration (hr)
Rapid Acting	Lispro Aspart Glulisine	Clear	15-30 min	SC or IV	15	1-3 (Shorter with meal)	2-5
Short Acting	Regular 100	Clear	30-60 min	SC or IV	30	2-3	4-6
Intermediate action	Neutral Protamine Hagedorn	Clear	1-2 hr	SC	N/A	4-8	10-20 24
Long acting	Detemir	Clear	2-4 hr	SC	N/A	6-8	6-24
	Glargine (U100. U300)		1-2 hr			"Peakless"	~24

Table (3)

*The time given depend on the source of data and intersubjective variability.
N/A: not applicable, SC; sub continuous, IV; Intravenous.

- Regular: U-500 (500 units/mL) is a concentrated being 5 times more potent than the 100 unit's/mL formulation, it is useful in patients who are severely insulin resistant requiring daily insulin doses of greater than 200 units/day because a large insulin dose may be given in a much smaller volume. it is recommended to be administered between 2 and 3 times daily
- Insulin Glargine: (U-100) provide a basal level of insulin.
  It can be administered any time during the day, but it is important to take it at the same time each day. It is usually administered at bedtime or, less commonly, in the morning.
  Advantage: less nocturnal hypoglycemia, once daily
  Disadvantage: associated with more injection site pain compared with NPH

- Insulin detemir: When used in Type 1 diabetes, two injections daily are usually required to provide adequate basal coverage due to a smaller insulin dose requirement in this patient population
- Premixed Insulin:

a. Formulation:

- Premixed NPH and regular insulin in a fixed ratio of 70:30 is available from as Humulin 70/30 and as Novolin 70/30.
- Humalog Mix 75/25 and Humalog Mix 50/50 are products with lispro protamine and insulin lispro in a fixed ratio of 75:25 and 50:50, respectively
- NovoLog Mix 70/30 is aspart protamine and insulin aspart in a fixed ratio of 70:30.
- These premixed insulins are useful for patients who have difficulty measuring and mixing insulins and are dosed twice daily.
- Avoid using it for type 1 unless no other choices

3- Side effect:

- Severe hypoglycemia
- Antibody development (adults: 3% to 28%; children and adolescents: 3%)
- Lipoatrophy at injection site (children and adolescents: 2%; adults: <1%)
- Weight gain
- Nasopharyngitis (20% to 24%), viral respiratory tract infection (children and adolescents: 21% to 23%)

4- Insulins storage: (Refer to companies' instructions)

Vial	Pen
Before use: Store in refrigerator 2° – 8° C	**Before use:** Store in refrigerator 2° – 8° C
After Use: Store in room temperature below 25°-30° C for 3-6 weeks	**After Use:** Store in room temperature below 25°-30° C for 3-6 weeks

Table (4)

Metformin:

a. Efficacy:

- (1%–2%) A1C reduction
- Lowers FPG concentrations 50 to 70 mg/dL
- Modestly lowers total cholesterol and triglycerides and may maintain or improve HDL-C levels

b. Weight:

- Weight loss of 0.5 to 3.8 kg

c. Side Effect:

- No hypoglycemia
- Common: Nausea, vomiting, diarrhea, epigastric pain, metallic taste, flatulence and anorexia.
- Less common: Decrease in vitamin B12 concentrations (monitor periodically).
- Lactic acidosis (rare): nausea, vomiting, increased respiratory rate, abdominal pain, shock, and tachycardia.

d. Contraindications:

- Renal impairment (contraindicated because of increased risk of lactic acidosis)

  Historically contraindicated if SCr ≥1.5 mg/dL in men and ≥1.4 mg/dL in women or reduced creatinine clearance (CrCl).

  In 2016, the FDA suggested that eGFR be used as a measure of kidney function rather than creatinine alone.

  Discontinue if eGFR is less than 30 mL/minute/1.73 m^2, **don't initiate** if eGFR is 30–45 mL/minute/1.73 m^2 and **don't discontinue** if eGFR is 30–45 mL/minute/1.73 m^2 and the patient already on it.
- Age 80 years or older (use caution and carefully assess renal function).
- High risk of cardiovascular event or hypoxic state.
- Hepatic impairment.
- Congestive heart failure (especially if prone to exacerbations)
- Interrupt therapy in patients with eGFR of 30–60 mL/minute/1.73 m^2 if undergoing procedures using iodinated contrast dye because of risk of nephrotoxicity. Reinitiate after 48 hours and after normal eGFR concentrations are achieved.
- DKA, Sepsis, Shock, Alcohol, Dehydration.
- Metformin could be a major factor related to vitamin B12 deficiency, whereas concurrent supplementation of multivitamins may potentially protect against the deficiency.

e. Drug-Drug Interaction:

- Dofetilide should not be administered in patients taking metformin due to the competition for common renal tubular transport systems, which may result in an increase in the plasma concentrations of either drug.
- Topiramate should be avoided in patients on metformin because topiramate may increase the risk of developing lactic acidosis.
- Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Metformin
- Thiazide and Thiazide-Like Diuretics: May diminish the therapeutic effect of Antidiabetic Agents.
- All patient's medication should be evaluated even if not mentioned above by referring to drug references.

f. Dose:
- To minimize GI side effects, metformin should be initiated at 500 mg twice a day or 850 mg once a day, to be taken with food, followed by weekly increases in 500 mg increments or 850mg increases every 2 weeks.
- 2 to 3 times daily (500–1,000 mg/dose; maximal dose 2,550 mg/day or 850 mg by mouth 3 times a day .
- Extended release once daily with evening meal.
- Not exceed 1,000 mg/day if GFR < 45.

Sulfonylureas: Glimepiride and Gliclazide:

a. Efficacy:
- 1%–2% A1C reduction

b. Weight:
- Increase: 2kgs

a. Side Effect:
- Severe hypoglycemia
- Rare: GI symptoms (nausea, fullness, bloating that can be relieved if taken with meals), rare blood dyscrasias, allergic dermatologic, photosensitivity, hepatotoxicity and hyponatremia

b. Contraindications:
- Type 1 diabetes.
- Pregnancy or breast-feeding, because these agents (except glyburide) can cross the placental barrier and can be excreted into breast milk
- Documented hypersensitivity to sulfonylureas.
- Severe hepatic or renal dysfunction; Poor renal function in older adults or in those with renal impairment because drug or active metabolites are not renally eliminated).
- Severe, acute intercurrent illness (e.g., infection, MI), surgery, or other stress that can unduly affect BG control, in which case insulin therapy should be used.
- G6PD deficiency—Patients with this deficiency may be at risk for hemolytic anemia if they take chlorpropamide—consider using a nonsulfonylurea medication as an alternative.
- Patients with hypoglycemic unawareness

c. Drug-Drug Interaction:
- CYP2C9
- Antidiabetic Agents: May enhance the hypoglycemic effect of Hypoglycemia-Associated Agents.
- Beta-Blockers: May enhance the hypoglycemic effect of Sulfonylureas. Cardioselective beta-blockers (eg, atenolol and metoprolol) may be safer than nonselective beta-

blockers. All beta-blockers appear to mask tachycardia as an initial symptom of hypoglycemia. Ophthalmic beta-blockers are probably associated with lower risk than systemic agents

- Thiazolidinedione, DPP4, (SGLT2) Inhibitors and Glucagon-Like Peptide-1 Agonists: May enhance the hypoglycemic effect of Sulfonylureas. Management: Consider a decrease in sulfonylurea dose when initiating therapy with a other antidiabetic agents and monitor patients for hypoglycemia.
- Thiazide and Thiazide-Like Diuretics: May diminish the therapeutic effect of Antidiabetic Agents.
- All patient's medication should be evaluated even if not mentioned above by referring to drug references.

d. Dose:

- Gliclazide:
  - Extended release 30 mg adjusted q2-4 week's max. 120mg
  - 30 mg extended = 80 mg immediate
- Glimepiride:
  - Initial dosage: 1-2mg once daily
  - Maximum daily dosage: 8mg

Thiazolidinedione (TZDs): Pioglitazone:

a. Efficacy: 0.5 %–1.4 % A1C reduction.

b. Weight:

- Increase weight gain 2-3 kgs (caused by fluid retention or fat accumulation)

c. Side Effect:

- Hepatotoxicity: increase LFT, should monitor every 3-6 moths in the first year then 6-12
- Hematologic: small decreases in hemoglobin and hematocrit and, infrequently, anemia
- Vascular and Cardiovascular: peripheral edema
- Pioglitazone: bladder cancer
- Increased risk of pancreatic and prostate cancer
- Increased risk of distal limb bone fractures (e.g., forearm, hand, wrist, foot, and ankle) and
- bone loss (older women and coadministration of steroid

d. Contraindications:

- Pioglitazone increased risk of angina and MI and all cause of mortality
- TZDs are contraindicated for use in patients with New York Heart Association (NYHA) (class III or IV) heart failure (HF) and are not recommended in patients with acute or systemic HF.
- TZDs should be used with caution in patients with preexisting edema, which may increase the risk of developing new-onset HF or exacerbating preexisting HF, or use with insulin increase risk of edema

- Hepatic impairment.
- Macular edema.

e. Drug-Drug Interaction:

- **Pioglitazone** is hepatically metabolized, mainly by CYP 2C8 and 3A4, and to a lesser degree by CYP1A1.
- Pioglitazone: estrogens, cyclosporine, tacrolimus, and βhydroxy-β-methylglutaryl-coenzyme **A (HMG-CoA)** reductase inhibitors.
- Patient on oral contraceptives or estrogen-replacement therapy should be informed of the possible risk of decreased effectiveness of estrogen therapy.
- **Gemfibrozil** significantly increases the Area Under the Curve (AUC) of pioglitazone. For patients receiving pioglitazone, **a dose reduction of the pioglitazone may be warranted.**
- Insulins: Pioglitazone may enhance the adverse/toxic effect of Insulins. Specifically, the risk for hypoglycemia, fluid retention, and heart failure may be increased with this combination. Management: If insulin is combined with pioglitazone, consider insulin dose reductions to avoid hypoglycemia. Monitor patients for fluid retention and signs/symptoms of heart failure, and consider pioglitazone dose reduction or discontinuation if heart failure occurs
- Sulfonylureas: Thiazolidinediones may enhance the hypoglycemic effect of Sulfonylureas. Management: Consider sulfonylurea dose adjustments in patients taking thiazolidinediones and monitor for hypoglycemia
- Pregabalin: May enhance the fluid-retaining effect of Thiazolidinediones.
- Thiazide and Thiazide-Like Diuretics: May diminish the therapeutic effect of Antidiabetic Agents.
- All patient's medication should be evaluated even if not mentioned above by referring to drug references.

f. Dose:

- No dose adjustment is necessary in patients with renal impairment.
- Should be avoided in patients with moderate-to severe hepatic impairment
- Pioglitazone: (a) Initial: 15 mg once daily, (b) Maximal daily dosage: 45 mg.
- Dosage titration is slow, and the maximal effect of a dosage change may not be observed for 8–12 weeks.
- The maximum dose of pioglitazone is 15 mg once a day if given with a strong CYP2C8 inhibitor: Gemfibrozil, trimethoprim and montleukast.

Incretin-Based Therapies (Glucagon-like Peptide-1 Agonists):

Once weekly injections Dulaglutide.

e. Efficacy:

- A 0.5%–1.5% reduction in A1C.

- Effects on postprandial hyperglycemia (60 to 70 mg/dL) better than on fasting glucose concentrations (5 to 25 mg/dl) with once- or twice-daily formulations.
- Improved A1C, fasting glucose reduction, and nausea or vomiting with once-weekly than with twice-daily exenatide formulation.
- Dulaglutide can reduce cardiovascular morbidity in patients with established cardiovascular disease

f. Weight:
- Weight loss (1.5–5 kgs).

g. Side Effect:
- Nausea, vomiting, and diarrhea.
- Hypoglycemic risk with insulin and sulphonylurea
- Rare: acute pancreatitis, and reduced renal function: severe abdominal pain accompanied by vomiting
- Development of antibodies (affect the A1C reduction)

h. Contraindications:
- Hypersensitivity.
- History of pancreatitis.
- Patients with severe GI disease.
- Dulaglutide has limited clinical experience in patients with end-stage renal disease and should be used with caution in these patients.
- If these patients experience GI adverse effects, renal function should be closely monitored, patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) and thyroid cancer due to risks in rodents (black box warnings).

i. Drug-Drug Interaction:
- Medication that require rapid GI absorption and are dose dependent on threshold concentrations for efficacy, such as antibiotics and oral contraceptives.
- Sulfonylureas: dulaglutide may enhance the hypoglycemic effect of Sulfonylureas
- Antidiabetic Agents may enhance the hypoglycemic effect of Hypoglycemia-Associated Agents.
- Insulins: Glucagon-Like Peptide-1 Agonists may enhance the hypoglycemic effect of Insulins. Management: Consider insulin dose reductions when used in combination with glucagon-like peptide-1 agonists.
- Thiazide and Thiazide-Like Diuretics: May diminish the therapeutic effect of Antidiabetic Agents
- All patient's medication should be evaluated even if not mentioned above by referring to drug references.

j. Dose:

- Starting patients on lower doses for daily injections, ensuring correct timing and administration of the drug, and titrating the dose slowly.
- Dulaglutide is 0.75 mg injected SC once weekly given at any time of the day and may be increased to 1.5 mg once weekly if the target not achieved.
- The insulin secretagogue (Sulfonylureas and Glinides) dose may need to be lowered (by about half) to reduce the risk of hypoglycemia.

Dipeptidyl Peptidase-4 Inhibitors: Sitagliptin, Linagliptin:

a. Efficacy:
   - Mainly used as add-on therapy.
   - 0.5%–0.8 % reduction A1C.
   - Sitagliptin, at a 100-mg dose, reduces dpp-4 activity by 80% for up to 24 hours.
   - Linagliptin, at the standard dose of 5 mg, has been shown to reduce dpp-4 activity by more than 80% for up to 24 hours.

b. Weight:
   - No effect.

c. Side Effect:
   - Sitagliptin: nasopharyngitis, upper respiratory tract infection, hypoglycemia, and headache.
   - Linagliptin: hypoglycemia, nasopharyngitis, diarrhea, and cough.
   - Increase risk for pancreatitis.

d. Contraindications:
   - All DPP-4 inhibitors should be avoided in patients with a history of serious hypersensitivity reaction to the drug

e. Drug-Drug Interaction:
   - Digoxin, a substrate of P-glycoprotein-like Sitagliptin, should be monitored for any signs or symptoms of digoxin toxicity, ketoconazole, Itraconazole, clarithromycin, Telithromycin, protease inhibitors such as Indinavir.
   - Rifampin decrease Linagliptin to levels that are sub-therapeutic (Rifampicin strong).
   - Insulins: Dipeptidyl Peptidase-4 Inhibitors may enhance the hypoglycemic effect of Insulins. Management: Consider a decrease in insulin dose when initiating therapy with a dipeptidyl peptidase-4 inhibitor and monitor patients for hypoglycemia.
   - Sulfonylureas: Dipeptidyl Peptidase-4 Inhibitors may enhance the hypoglycemic effect of Sulfonylureas. Management: Consider a decrease in sulfonylurea dose when initiating therapy with a dipeptidyl peptidase-4 inhibitor and monitor patients for hypoglycemia.
   - Thiazide and Thiazide-Like Diuretics: May diminish the therapeutic effect of Antidiabetic Agents.
   - Angiotensin-Converting Enzyme Inhibitors: Dipeptidyl Peptidase-4 Inhibitors may enhance the adverse/toxic effect of Angiotensin-Converting Enzyme Inhibitors. Specifically, the risk of angioedema may be increased.

- All patient's medication should be evaluated even if not mentioned above by referring to drug references.

e. Dose:

- Sitagliptin may be initiated at 100 mg taken once daily with or without food.
- (CrCl 30– 50 mL/minute)50 mg once daily, (CrCl <30 mL/minute) or for those in end-stage renal failure requiring dialysis, the Sitagliptin dose is 25 mg once daily regardless of the time of dialysis (as the company's instruction don't crush, split or chewed 100 mg tablet). Only one can be used in peritoneal dialysis, decrease the dose of insulin if start sitagliptin then adjusted.
- Linagliptin is dosed at 5 mg once daily with or without food. No dose adjustment is necessary for patients with renal impairment; however, patients with a CrCl <30 mL/minute may be more prone to hypoglycemia.
- The insulin secretagogue (Sulfonylureas and Glinid) dose may need to be lowered (by about half) to reduce the risk of hypoglycemia.

Sodium–Glucose Transporter 2 (SGLT2) Inhibitors: Empagliflozin

a. Efficacy:

- 0.3%–1.0 % reduction in A1C.
- Effect on both fasting and postprandial glucose concentrations.
- Empagliflozin can reduce cardiovascular morbidity in patients with established cardiovascular disease (FDA approved label).
- Empagliflozin can reduce the diabetic kidney disease.

b. Weight:

- Mild weight loss.

c. Side effect:

- Increased urination.
- Genital mycotic infections (more common in females).
- Hypotension.
- Increased hypoglycemia risk with concomitant insulin or insulin secretagogue.
- Class is linked with rare cases of ketoacidosis.

d. Contraindications:

- Significant renal impairment (varies by agent).
- Suggested to ensure euvolemia before initiating agent, given its diuretic effect especially in older adults' patient.

e. Drug- Drug interaction:

- Metoprolol: Empagliflozin may cause salt and water loss, which may increase the risk of dehydration and low blood pressure when used with metoprolol or similar medications.
- Thiazide and Thiazide-Like Diuretics: May diminish the therapeutic effect of Antidiabetic Agents.

- Insulin: Empagliflozin may help control blood glucose levels, which may lead to a reduction in your dosage requirement of insulin or any other diabetic medications you are receiving.
- Loop Diuretics: Empagliflozin may enhance the hypotensive effect of Loop Diuretics.
- Sulfonylureas: Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors may enhance the hypoglycemic effect of Sulfonylureas. Management: Consider a decrease in sulfonylurea dose when initiating therapy with a sodium-glucose cotransporter 2 inhibitor and monitor patients for hypoglycemia.
- All patient's medication should be evaluated even if not mentioned above by referring to drug references.

f. Dose:

- Initial, 10 mg orally once daily in the morning; may increase to 25 mg orally once daily; MAX 25 mg orally once daily
- In Renal impairment: Once Daily, eGFR :< 45 ml/min/1.73m2: Do not initiate.
- In Hepatic Impairment No dosage adjustment

D. Diabetes Complications [4,5]

Hypoglycemia Symptoms and Management

Hypoglycemia

Signs and Symptoms:

Blurred vision, sweaty palms, generalized sweating, tremulousness, hunger, confusion, anxiety, circumoral tingling, and numbness.

Patients vary with regard to their symptoms. Behavior can be confused with alcohol inebriation. Patients become combative and use poor judgment Nocturnal hypoglycemia: nightmares, restless sleep, profuse sweating, morning headache, morning "hangover." Not all patients have symptoms during nocturnal hypoglycemia

Classification of hypoglycemia:

Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L).
Level 2	Glucose <54 mg/dL (3.0 mmol/L).
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia.

Table (5)

Management of hypoglycemia

Clinical Considerations
Irregular eating patterns
↑ Physical exercise
Gastroparesis (delayed gastric emptying)
Defective counter-regulatory responses
Excessive dose of insulin or insulin secretagogues (Sulfonylureas, Glinides)
Alcohol& Drugs ingestion
Treatment
Ingest 10–20 g of rapidly absorbed carbohydrate. Repeat in 15–20 minutes if glucose concentration remains less than 70 mg/dL or if patient is symptomatic. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **(B)**
The following are examples of food sources that provide 15 g of carbohydrate:
Orange, grapefruit, or apple juice; regular, non-diet soda 1/2 cup
Fat-free milk 1 cup
Grape juice, cranberry juice cocktail 1/3 cup
Sugar 1 tbsp or 3 cubes
Lifesavers 5–6 pieces
Glucose tablets 3–4 tablets
If patient is unconscious, the following measures should be initiated
Glucagon 1 mg SC, IM (generally administered IM in outpatient setting; mean response time, 6.5 minutes) **(E)** Or Hospital admission (Refer to MOH guideline for management of hypoglycemia)

Table (6)

Other Considerations:

1. The key to successful management of hypoglycemia is recognition and prevention.
2. Because early warning symptoms of hypoglycemia vary from person to person, it is important the patient learn to recognize and pay attention to his earliest warning symptoms and treat early.
3. Encourage patients to test their BG level any time they "feel unusual" to verify a low BG concentration before treatment.

Diabetic ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS):

1- DKA more common in type 1 DM but can occur in type 2 DM: elevated plasma glucose concentrations (>250 mg/mL) with ketoacidosis

2- HHS common in type 2 DM: elevated plasma glucose concentrations (>600 mg/mL) and high serum osmolality (>320 mOsm/L) without ketoacidosis

3- Usually occurs because of a precipitating factor that stresses the body, resulting in increased counter regulatory hormones:
   - Inappropriate (including non-adherence) or inadequate insulin therapy and infection are the two most common causes.
   - Other causes: Myocardial infarction, pancreatitis, stroke, drugs (e.g., corticosteroids)

4- Results in significant hyperglycemia, dehydration, and ketoacidosis.

Symptoms and Signs:

Polyuria, polydipsia, vomiting, dehydration, weakness, abdominal pain, tachycardia, hyponatremia, hyperkalemia, mental alteration. HHS usually associated with altered consciousness varying from confusion or disorientation to coma, usually as a result of extreme dehydration with or without prerenal azotemia, hyperglycemia, and hyperosmolality. In contrast to DKA, focal or generalized seizures and transient hemiplegia may occur.

Treatment:

1. Advice the patients about re-hydration.
2. Hospital admission (Refer to MOH guideline for management of DKA/HHS)

Somogyi phenomena:

1. Also known as "rebound hyperglycemia" and named after the physician who first described it, the Somogyi effect is a pattern of undetected hypoglycemia (low blood glucose values of less than 70) followed by hyperglycemia (high blood glucose levels of more than 200).

2. Typically, this happens in the middle of the night, but can also occur when too much insulin is circulating in the system. The cause of the Somogyi effect is said to be “man-made” that is, a result of insulin or diabetes pills working too strongly at the wrong time.
3. This refers to a swing to a high level of glucose (sugar) in the blood from an extremely low level, usually occurring after an un-recognized and therefore an untreated insulin reaction and hypoglycemic attack during sleep in the early hours of the morning or during the night. It presents as hyperglycemia before breakfast.
4. People who experience high levels of blood glucose in the morning may need to test their blood glucose levels in the middle of the night. If blood glucose levels are falling or low, adjustments in evening snacks or insulin doses may be recommended.
5. It is essential to recognize the Somogyi effect in order to avoid the mistake of increasing (rather than reducing) the dose of insulin in this situation.

Dawn Phenomenon:

1. The Dawn Phenomenon refers to a sudden rise in blood glucose levels in the early morning hours.
2. The dawn phenomenon is a surge of hormones that the body produces daily around 4:00 a.m. to 5:00 a.m.
3. People with diabetes don't have normal insulin responses to adjust for this, and may see their fasting glucose go up.
4. The rise in glucose is mostly because the body is making less insulin and more glucagon (a hormone that increases blood glucose) than it needs. The less insulin made by the pancreas, the more glucagon the pancreas makes as a result. Glucagon signals the liver to break down glycogen into glucose. This is why high fasting blood glucose levels are common in people with type 2.
5. Unlike the Somogyi effect, it is not a result of an insulin reaction.
6. People who have high levels of blood glucose in the mornings before eating may need to monitor their blood glucose during the night.
7. If blood glucose levels are rising, adjustments in evening snacks or insulin dosages may be recommended.

Consideration for chronic complications [3]:

- **Chronic cardiovascular complications recommendation:**
  - Antiplatelet

a. Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **(A)**
b. For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **(B)**

c. Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. **(A)**
d. The presence of retinopathy is not a contraindication to aspirin therapy for cardio protection, as aspirin does not increase the risk of retinal hemorrhage.
e. Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome **(A)** and may have benefits beyond this period **(B)**

➢ Hypertension

a. Hypertension, defined as a sustained blood pressure ≥140/90 mmHg, is common among patients with either type 1 or type 2 diabetes.
b. Hypertension is a major risk factor for both ASCVD and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications.
c. For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences.
d. For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease [ASCVD] or 10-year ASCVD risk ≥15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely attained. **(C)**
e. For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a blood pressure target of <140/90 mmHg. **(A)**
f. In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of ≤135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension **(A)** and minimizing impaired fetal growth **(E)**
g. Patients with confirmed office-based blood pressure ≥140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. **(A)**
h. Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. **(A)**
i. Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes ACE inhibitors (captopril, enalapril and perindopril), angiotensin receptor blockers (valsartan and telmisartan) , thiazide-like diuretics (hydrochlorothiazide), or dihydropyridine calcium channel blocker (amlodipine). **(A)**

j. Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. **(A)**
k. An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine (**A)** or 30–299 mg/g creatinine **(B)**. If one class is not tolerated, the other should be substituted. **(B)**
l. For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. **(B)**
m. Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy (aldosterone). **(B)**

➢ <u>Dyslipidemia</u>

a. In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. **(E)**
b. Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication adherence. **(E)**
c. Statin treatment as primary prevention:
   - For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. **(A)**
   - For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **(C)**
   - In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy. **(B)**
   - In adults with diabetes and 10-year atherosclerotic cardiovascular disease risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more. **(C)**
d. Statin treatment as Secondary Prevention:
   - For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. **(A)**
   - For patients with diabetes and atherosclerotic cardiovascular disease considered very high risk using specific criteria, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor).**(A)** Ezetimibe may be preferred due to lower cost.
   - For patients who do not tolerate the intended intensity, the maximally tolerated statin dose should be used. **(E)**

- In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment. **(B)**
- In adults with diabetes aged >75 years, it may be reasonable to initiate statin therapy after discussion of potential benefits and risks. **(C)**

e. Statin therapy is contraindicated in pregnancy. **(B)**

- **Chronic micro-complications recommendation:**
  - Chronic kidney disease

a. At least once a year, assess urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate (eGFR) in patients with type 1 diabetes with duration of ≥5 years and in all patients with type 2 diabetes regardless of treatment. **(B)** Patients with urinary albumin >30 mg/g creatinine and/or an eGFR <60 mL/min/1.73 m2 should be monitored twice annually to guide therapy. **(C)**

b. In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) **(B)** and is strongly recommended for those with urinary albumin-to-creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. **(A)**

c. Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. **(B)**

d. An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. **(A)**

e. Patients should be referred for evaluation by a nephrologist if they have an estimated glomerular filtration rate <30 mL/min/1.73 m2. **(A)**

- Diabetic neuropathy:

a. Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes **(A)** and to slow the progression of neuropathy in patients with type 2 diabetes Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications **(B)**

b. Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **(A)**

c. Recommendation about using of vitamin B complex may be considered for neuropathic symptomatic patients especially for patients on metformin. **(E)**

- Diabetic retinopathy:

a. Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **(A)**

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Ministry of Health

Appendix 1: Drug-Drug interaction
The updating drug –drug interaction will be available in MOH-Formulary

Metformin:

Drugs:	**Severity**:	**Summary**:
Metformin [Systemic] -- Iobitridol [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iobitridol And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iodipamide [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iodipamide And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Ioxaglate [Injection (Systemic)] -- Metformin [Systemic]	Contraindicated	Concurrent Use Of Ioxaglate And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Ioglicic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Ioglicic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Metrizoic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Metrizoic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iocarmic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iocarmic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iotroxic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iotroxic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iomeprol [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iomeprol And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iothalamate [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iothalamate And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iophendylate [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iophendylate And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iobenzamic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iobenzamic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iopronic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iopronic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iodopyracet [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iodopyracet And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Ioxitalamic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Ioxitalamic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iocetamic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iocetamic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Tyropanoate Sodium [Injection (Systemic)]	Contraindicated	Concurrent Use Of Tyropanoate Sodium And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iodoxamic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iodoxamic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Ipodate [Injection (Systemic)]	Contraindicated	Concurrent Use Of Ipodate And Metformin May Result In Lactic Acidosis And Acute Renal Failure.

Metformin [Systemic] -- Iodixanol [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iodixanol And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Iohexol [Injection (Systemic)] -- Metformin [Systemic]	Contraindicated	Concurrent Use Of Iohexol And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Iopamidol [Injection (Systemic)] -- Metformin [Systemic]	Contraindicated	Concurrent Use Of Iopamidol And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iotasul [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iotasul And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Diatrizoate [Injection (Systemic)]	Contraindicated	Concurrent Use Of Diatrizoate And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Ioglycamic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Ioglycamic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Ethiodized Oil [Injection (Systemic)]	Contraindicated	Concurrent Use Of Ethiodized Oil And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iodamide [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iodamide And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metrizamide [Injection (Systemic)] -- Metformin [Systemic]	Contraindicated	Concurrent Use Of Metrizamide And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iopentol [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iopentol And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iopromide [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iopromide And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Acetrizoic Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Acetrizoic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iosimide [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iosimide And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iotrolan [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iotrolan And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Iopanoic Acid [Injection (Systemic)] -- Metformin [Systemic]	Contraindicated	Concurrent Use Of Iopanoic Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Ioseric Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Ioseric Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Iodohippuric Acid [Injection (Systemic)]	Contraindicated	Concurrent Use Of Iodohippuric Acid And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Metformin [Systemic] -- Dolutegravir [Systemic]	Major	Concurrent Use Of Dolutegravir And Metformin May Result In Increased Metformin Exposure.
Metformin [Systemic] -- Vandetanib [Systemic]	Major	Concurrent Use Of Metformin And Vandetanib May Result In Increased Metformin Exposure.
Metformin [Systemic] -- Dasabuvir [Systemic]	Major	Concurrent Use Of Dasabuvir And Metformin May Result In Increased Risk Of Lactic Acidosis.
Aspirin -- Oral Hypoglycemics	Major	Concurrent Use Of Aspirin And Oral Hypoglycemics May Result In Increased Risk Of Hypoglycemia.
Antidiabetic Agents -- Somatostatin Analogues	Major	Concurrent Use Of Antidiabetic Agents And Somatostatin Analogues May Result In Impaired Glucose Regulation.

Metformin Hydrochloride Interact(S) With: Interacting Substances		
Metformin [Systemic] -- Ritonavir [Systemic]	**Major**	Concurrent Use Of Metformin And Ritonavir May Result In Increased Risk Of Lactic Acidosis.
Chloroquine -- Antidiabetic Agents	**Major**	Concurrent Use Of Chloroquine And Antidiabetic Agents May Result In Hypoglycemia.
Sitagliptin -- Insulin Secretagogues	**Major**	Concurrent Use Of Sitagliptin And Insulin Secretagogues May Result In Increased Risk Of Hypoglycemia.
Metformin [Systemic] -- Ombitasvir [Systemic]	**Major**	Concurrent Use Of Metformin And Ombitasvir May Result In Increased Risk Of Lactic Acidosis.
Fluoroquinolones -- Antidiabetic Agents	**Major**	Concurrent Use Of Fluoroquinolones And Antidiabetic Agents May Result In Changes In Blood Glucose And Increased Risk Of Hypoglycemia Or Hyperglycemia.
Metformin Hydrochloride Interact(S) With: Interacting Substances		
Pioglitazone -- Insulin Secretagogues	**Major**	Concurrent Use Of Pioglitazone And Insulin Secretagogues May Result In Increased Risk Of Hypoglycemia.
Bupropion -- Oct2 Substrates	**Major**	Concurrent Use Of Bupropion And Oct2 Substrates May Result In Reduced Renal Clearance Of Oct2 Substrates.
Metformin [Systemic] -- Dofetilide [Systemic]	**Major**	Concurrent Use Of Dofetilide And Metformin May Result In An Increased Risk Of Cardiotoxicity (Qt Prolongation, Torsades De Pointes, Cardiac Arrest).
Hydroxychloroquine -- Antidiabetic Agents	**Major**	Concurrent Use Of Hydroxychloroquine And Antidiabetic Agents May Result In Hypoglycemia.
Thioctic Acid -- Antidiabetic Agents	**Major**	Concurrent Use Of Thioctic Acid And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Tafenoquine -- Oct2 And Mate Substrates	**Major**	Concurrent Use Of Tafenoquine And Oct2 And Mate Substrates May Result In Increased Plasma Concentrations Of Oct2 And Mate Substrates.
Metformin [Systemic] -- Paritaprevir [Systemic]	**Major**	Concurrent Use Of Metformin And Paritaprevir May Result In Increased Risk Of Lactic Acidosis.
Capmatinib -- Mate1 And Mate2k Substrates	**Major**	Concurrent Use Of Capmatinib And Mate1 And Mate2k Substrates May Result In Increased Exposure Of Mate1 And Mate2k Substrates And Risk Of Increased Adverse Reactions.
Ioversol [Systemic] -- Metformin [Systemic]	**Major**	Concurrent Use Of Ioversol And Metformin May Result In Lactic Acidosis And Acute Renal Failure.
Rifampin [Systemic] -- Metformin [Systemic]	**Moderate**	Concurrent Use Of Metformin And Rifampin May Result In Increased Metformin Plasma Concentrations; Enhanced Glucose Lowering Effects Of Metformin.
Metformin [Oral (Systemic)] -- Patiromer [Oral (Systemic)]	**Moderate**	Concurrent Use Of Metformin And Patiromer May Result In Decreased Metformin Exposure.
Verapamil [Systemic] -- Metformin [Systemic]	**Moderate**	Concurrent Use Of Metformin And Verapamil May Result In Decreased Glucose-Lowering Effect Of Metformin.
Fenugreek -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Fenugreek And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.

Metformin [Systemic] -- Guar Gum [Systemic]	**Moderate**	Concurrent Use Of Metformin And Guar Gum May Result In Decreased Effectiveness Of Metformin.
Metformin [Systemic] -- Ranolazine [Systemic]	**Moderate**	Concurrent Use Of Metformin And Ranolazine May Result In Increased Metformin Exposure.
Monoamine Oxidase Inhibitors -- Selected Antidiabetic Agents **Metformin Hydrochloride Interact(S) With:**Interacting Substances	**Moderate**	Concurrent Use Of Monoamine Oxidase Inhibitors And Selected Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Metformin [Systemic] -- Colesevelam [Systemic]	**Moderate**	Concurrent Use Of Colesevelam And Metformin May Result In Increased Exposure To Extended-Release Metformin.
Psyllium -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Psyllium And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Bitter Melon -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Bitter Melon And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Antidiabetic Agents -- Beta-Adrenergic Blockers **Metformin Hydrochloride Interact(S) With:** Interacting Substances	**Moderate**	Concurrent Use Of Antidiabetic Agents And Beta-Adrenergic Blockers May Result In Hypoglycemia Or Hyperglycemia; Decreased Symptoms Of Hypoglycemia.
Glucomannan -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Glucomannan And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Insulin Or Pramlintide -- Oral Antidiabetic Agents **Metformin Hydrochloride Interact(S) With:** Interacting Substances	**Moderate**	Concurrent Use Of Insulin Or Pramlintide And Oral Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Licorice -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Licorice And Antidiabetic Agents May Result In Reduced Antidiabetic Agent Effectiveness.
Gymnema Sylvestre -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Gymnema Sylvestre And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Eucalyptus -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Eucalyptus And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Semaglutide -- Insulin Secretagogues And Insulins	**Moderate**	Concurrent Use Of Semaglutide And Insulin Secretagogues And Insulins May Result In Increased Risk Of Hypoglycemia.
Digoxin [Systemic] -- Metformin [Systemic]	**Moderate**	Concurrent Use Of Digoxin And Metformin May Result In Increased Digoxin Concentrations.
Ginseng -- Antidiabetic Agents	**Moderate**	Concurrent Use Of Ginseng And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.
Exenatide -- Insulin Secretagogues	**Moderate**	Concurrent Use Of Exenatide And Insulin Secretagogues May Result In Increased Risk Of Hypoglycemia.
Ace Inhibitors -- Antidiabetic Agents **Metformin Hydrochloride**	**Moderate**	Concurrent Use Of Ace Inhibitors And Antidiabetic Agents May Result In Increased Risk Of Hypoglycemia.

Interact(S) With: Interacting Substances		
Glucosamine -- Antidiabetic Agents	**Minor**	Concurrent Use Of Glucosamine And Antidiabetic Agents May Result In Reduced Antidiabetic Agent Effectiveness.

Sulfonylurea:

Drugs:	Severity:	Summary:
Metreleptin -- Insulin Secretagogues	**Major**	Concurrent use of METRELEPTIN and INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Dulaglutide -- Selected Sulfonylureas	**Major**	Concurrent use of DULAGLUTIDE and SELECTED SULFONYLUREAS may result in increased risk of hypoglycemia.
Isoniazid [Systemic] -- Glimepiride [Systemic]	**Major**	Concurrent use of GLIMEPIRIDE and ISONIAZID may result in increased glimepiride exposure and risk of hypoglycemia.
Voriconazole [Systemic] -- Glimepiride [Systemic]	**Major**	Concurrent use of GLIMEPIRIDE and VORICONAZOLE may result in increased risk of hypoglycemia.
Disopyramide -- Sulfonylureas	**Major**	Concurrent use of DISOPYRAMIDE and SULFONYLUREAS may result in increased risk of hypoglycemia.
Desmopressin -- Sulfonylureas	**Major**	Concurrent use of DESMOPRESSIN and SULFONYLUREAS may result in increased risk of hyponatremia.
MICONAZOLE [Oral (Systemic)] -- GLIMEPIRIDE [Systemic]	**Major**	Concurrent use of GLIMEPIRIDE and MICONAZOLE may result in severe hypoglycemia.
Aspirin -- Oral Hypoglycemics	**Major**	Concurrent use of ASPIRIN and ORAL HYPOGLYCEMICS may result in increased risk of hypoglycemia.
Antidiabetic Agents -- Somatostatin Analogues **Glimepiride Interact(S) With:Interacting Substances**	**Major**	Concurrent use of ANTIDIABETIC AGENTS and SOMATOSTATIN ANALOGUES may result in impaired glucose regulation.
Chloroquine -- Antidiabetic Agents	**Major**	Concurrent use of CHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Sitagliptin -- Insulin Secretagogues	**Major**	Concurrent use of SITAGLIPTIN and INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Fluoroquinolones -- Antidiabetic Agents **Glimepiride Interact(S) With:Interacting Substances**	**Major**	Concurrent use of FLUOROQUINOLONES and ANTIDIABETIC AGENTS may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.
Pioglitazone -- Insulin Secretagogues	**Major**	Concurrent use of PIOGLITAZONE and INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Hydroxychloroquine -- Antidiabetic Agents	**Major**	Concurrent use of HYDROXYCHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Lixisenatide -- Sulfonylureas	**Major**	Concurrent use of LIXISENATIDE and SULFONYLUREAS may result in increased risk of hypoglycemia .
Thioctic Acid -- Antidiabetic Agents	**Major**	Concurrent use of THIOCTIC ACID and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.

Entacapone [Systemic] -- Glimepiride [Systemic]	Major	Concurrent use of ENTACAPONE and GLIMEPIRIDE may result in increased glimepiride exposure.
Porfimer -- Photosensitizing Agents	Major	Concurrent use of PORFIMER and PHOTOSENSITIZING AGENTS may result in excessive intracellular damage in photosensitized tissues.
Fenugreek -- Antidiabetic Agents	Moderate	Concurrent use of FENUGREEK and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Saxagliptin -- Insulin And Insulin Secretagogues	Moderate	Concurrent use of SAXAGLIPTIN and INSULIN AND INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Guar Gum -- Antidiabetic Agents	Moderate	Concurrent use of GUAR GUM and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Colesevelam [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of COLESEVELAM and GLIMEPIRIDE may result in decreased glimepiride exposure.
Monoamine Oxidase Inhibitors -- Selected Antidiabetic Agents Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of MONOAMINE OXIDASE INHIBITORS and SELECTED ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Aminolevulinic Acid -- Phototoxic Drugs	Moderate	Concurrent use of AMINOLEVULINIC ACID and PHOTOTOXIC DRUGS may result in increased risk of phototoxic skin reaction (ie, severe sunburn).
Psyllium -- Antidiabetic Agents	Moderate	Concurrent use of PSYLLIUM and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Bitter Melon -- Antidiabetic Agents	Moderate	Concurrent use of BITTER MELON and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Antidiabetic Agents -- Beta-Adrenergic Blockers Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of ANTIDIABETIC AGENTS and BETA-ADRENERGIC BLOCKERS may result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.
Glucomannan -- Antidiabetic Agents	Moderate	Concurrent use of GLUCOMANNAN and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Chloramphenicol [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and CHLORAMPHENICOL may result in hypoglycemia.
Amiodarone [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of AMIODARONE and GLIMEPIRIDE may result in increased plasma levels of glimepiride.
Propoxyphene [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and PROPOXYPHENE may result in increased blood glucose lowering effect and increased risk of hypoglycemia.
Insulin Or Pramlintide -- Oral Antidiabetic Agents Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of INSULIN OR PRAMLINTIDE and ORAL ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Glimepiride -- Anabolic Steroids Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of GLIMEPIRIDE and ANABOLIC STEROIDS may result in increased blood glucose lowering effect and increased risk of hypoglycemia.
Linagliptin -- Insulin Secretagogues	Moderate	Concurrent use of LINAGLIPTIN and INSULIN SECRETAGOGUES may result in an increased risk of hypoglycemia.

Antidiabetic Agents -- Selected Diuretics Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of ANTIDIABETIC AGENTS and SELECTED DIURETICS may result in increased hyperglycemia risk; increased insulin requirement.
Glimepiride -- Fibrates Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of GLIMEPIRIDE and FIBRATES may result in increased glimepiride exposure and increased blood glucose lowering effect and risk of hypoglycemia.
Licorice -- Antidiabetic Agents	Moderate	Concurrent use of LICORICE and ANTIDIABETIC AGENTS may result in reduced antidiabetic agent effectiveness.
Gymnema Sylvestre -- Antidiabetic Agents	Moderate	Concurrent use of GYMNEMA SYLVESTRE and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Phenprocoumon [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and PHENPROCOUMON may result in excessive hypoglycemia.
Dicumarol [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of DICUMAROL and GLIMEPIRIDE may result in excessive hypoglycemia.
Eucalyptus -- Antidiabetic Agents	Moderate	Concurrent use of EUCALYPTUS and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Acenocoumarol [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of ACENOCOUMAROL and GLIMEPIRIDE may result in excessive hypoglycemia.
Semaglutide -- Insulin Secretagogues And Insulins	Moderate	Concurrent use of SEMAGLUTIDE and INSULIN SECRETAGOGUES AND INSULINS may result in increased risk of hypoglycemia.
Guanethidine [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and GUANETHIDINE may result in increased blood glucose lowering effect and risk of hypoglycemia.
Glimepiride -- Histamine H(2)-Receptor Antagonists Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of GLIMEPIRIDE and HISTAMINE H(2)-RECEPTOR ANTAGONISTS may result in increased blood glucose lowering effect and increased risk of hypoglycemia.
Fluoxetine [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of FLUOXETINE and GLIMEPIRIDE may result in excessive hypoglycemia.
Sulfinpyrazone [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and SULFINPYRAZONE may result in increased blood glucose lowering effect and increased risk of hypoglycemia.
Antidiabetic Agents -- Sulfonamides Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of ANTIDIABETIC AGENTS and SULFONAMIDES may result in increased risk of hypoglycemia.
Ginseng -- Antidiabetic Agents	Moderate	Concurrent use of GINSENG and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Mifepristone [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and MIFEPRISTONE may result in increased exposure to glimepiride.
Probenecid [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and PROBENECID may result in hypoglycemia.
Exenatide -- Insulin Secretagogues	Moderate	Concurrent use of EXENATIDE and INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Warfarin [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and WARFARIN may result in excessive hypoglycemia.

Pentoxifylline [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of GLIMEPIRIDE and PENTOXIFYLLINE may result in increased blood glucose lowering effect and increased risk of hypoglycemia.
Glimepiride -- Androgens Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of GLIMEPIRIDE and ANDROGENS may result in increased blood glucose lowering effect and increased risk of hypoglycemia.
Clarithromycin [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of CLARITHROMYCIN and GLIMEPIRIDE may result in Increased risk of hypoglycemia.
Cyclophosphamide [Systemic] -- Glimepiride [Systemic]	Moderate	Concurrent use of CYCLOPHOSPHAMIDE and GLIMEPIRIDE may result in increased blood glucose lowering effect and risk of hypoglycemia.
Glimepiride -- Tetracyclines Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of GLIMEPIRIDE and TETRACYCLINES may result in increased blood glucose lowering effect and increased risk of hypoglycemia.
Empagliflozin -- Insulin Secretagogues	Moderate	Concurrent use of EMPAGLIFLOZIN and INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Ace Inhibitors -- Antidiabetic Agents Glimepiride Interact(S) With:Interacting Substances	Moderate	Concurrent use of ACE INHIBITORS and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Fluvoxamine [Systemic] -- Glimepiride [Systemic]	Minor	Concurrent use of FLUVOXAMINE and GLIMEPIRIDE may result in an increase in plasma concentrations of glimepiride.
Rifampin [Systemic] -- Glimepiride [Systemic]	Minor	Concurrent use of GLIMEPIRIDE and RIFAMPIN may result in decreased glimepiride plasma concentrations.
Glucosamine -- Antidiabetic Agents	Minor	Concurrent use of GLUCOSAMINE and ANTIDIABETIC AGENTS may result in reduced antidiabetic agent effectiveness.

Pioglitazone:

Drugs:	Severity:	Summary:
Nifedipine -- Cyp3a4 Inducers	Major	Concurrent use of NIFEDIPINE and CYP3A4 INDUCERS may result in decreased NIFEdipine exposure.
Antidiabetic Agents -- Somatostatin Analogues Pioglitazone Hydrochloride Interact(S) With:Interacting Substances	Major	Concurrent use of ANTIDIABETIC AGENTS and SOMATOSTATIN ANALOGUES may result in impaired glucose regulation.
Pioglitazone [Systemic] -- Tolvaptan [Systemic]	Major	Concurrent use of PIOGLITAZONE and TOLVAPTAN may result in decreased tolvaptan plasma concentrations.
Chloroquine -- Antidiabetic Agents	Major	Concurrent use of CHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Fluoroquinolones -- Antidiabetic Agents Pioglitazone Hydrochloride	Major	Concurrent use of FLUOROQUINOLONES and ANTIDIABETIC AGENTS may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.

Interact(S) With:Interacting Substances		
Pioglitazone -- Insulin Secretagogues **Pioglitazone Hydrochloride Interact(S) With:Interacting Substances**	**Major**	Concurrent use of PIOGLITAZONE and INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Insulin -- Peroxisome Proliferator-Activated Receptor (Ppar)-Gamma Agonists **Pioglitazone Hydrochloride Interact(S) With:Interacting Substances**	**Major**	Concurrent use of INSULIN and PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR)-GAMMA AGONISTS may result in increased risk of fluid retention and heart failure; increased risk of hypoglycemia.
Hydroxychloroquine -- Antidiabetic Agents	**Major**	Concurrent use of HYDROXYCHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Ifosfamide [Systemic] -- Pioglitazone [Systemic]	**Major**	Concurrent use of IFOSFAMIDE and PIOGLITAZONE may result in increased neurotoxic and nephrotoxic effects.
Thioctic Acid -- Antidiabetic Agents	**Major**	Concurrent use of THIOCTIC ACID and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Lumateperone -- Cyp3a4 Inducers	**Major**	Concurrent use of LUMATEPERONE and CYP3A4 INDUCERS may result in decreased lumateperone exposure.
Pixantrone -- Cyp2c8 Substrates	**Major**	Concurrent use of PIXANTRONE and CYP2C8 SUBSTRATES may result in increased exposure of CYP2C8 substrates.
Piperaquine -- Cyp3a4 Inducers	**Major**	Concurrent use of PIPERAQUINE and CYP3A4 INDUCERS may result in decreased exposure of piperaquine.
Rifampin [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of PIOGLITAZONE and RIFAMPIN may result in decreased pioglitazone exposure.
Clopidogrel [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of CLOPIDOGREL and PIOGLITAZONE may result in increased exposure of pioglitazone.
Ketoconazole [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of KETOCONAZOLE and PIOGLITAZONE may result in increased pioglitazone serum concentrations and increased risk of hypoglycemia (CNS depression, seizures, diaphoresis, tachypnea, tachycardia, hypothermia).
Fenugreek -- Antidiabetic Agents	**Moderate**	Concurrent use of FENUGREEK and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Pioglitazone [Systemic] -- Nilotinib [Systemic]	**Moderate**	Concurrent use of NILOTINIB and PIOGLITAZONE may result in altered exposure to pioglitazone.
Atorvastatin [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of ATORVASTATIN and PIOGLITAZONE may result in decreased pioglitazone serum concentrations.
Guar Gum -- Antidiabetic Agents	**Moderate**	Concurrent use of GUAR GUM and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Topiramate [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of PIOGLITAZONE and TOPIRAMATE may result in decreased pioglitazone exposure.
Psyllium -- Antidiabetic Agents	**Moderate**	Concurrent use of PSYLLIUM and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Bitter Melon -- Antidiabetic Agents	**Moderate**	Concurrent use of BITTER MELON and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.

Antidiabetic Agents -- Beta-Adrenergic Blockers **Pioglitazone Hydrochloride Interact(S) With:Interacting Substances**	**Moderate**	Concurrent use of ANTIDIABETIC AGENTS and BETA-ADRENERGIC BLOCKERS may result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.
Glucomannan -- Antidiabetic Agents	**Moderate**	Concurrent use of GLUCOMANNAN and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Pioglitazone -- Protease Inhibitors **Pioglitazone Hydrochloride Interact(S) With:Interacting Substances**	**Moderate**	Concurrent use of PIOGLITAZONE and PROTEASE INHIBITORS may result in worsening glycemic control.
Pioglitazone [Systemic] -- Atazanavir [Systemic]	**Moderate**	Concurrent use of ATAZANAVIR and PIOGLITAZONE may result in loss of glycemic control or increased pioglitazone exposure.
Antidiabetic Agents -- Selected Diuretics **Pioglitazone Hydrochloride Interact(S) With:Interacting Substances**	**Moderate**	Concurrent use of ANTIDIABETIC AGENTS and SELECTED DIURETICS may result in increased hyperglycemia risk; increased insulin requirement.
Licorice -- Antidiabetic Agents	**Moderate**	Concurrent use of LICORICE and ANTIDIABETIC AGENTS may result in reduced antidiabetic agent effectiveness.
Gymnema Sylvestre -- Antidiabetic Agents	**Moderate**	Concurrent use of GYMNEMA SYLVESTRE and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Eucalyptus -- Antidiabetic Agents	**Moderate**	Concurrent use of EUCALYPTUS and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Nimodipine [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of NIMODIPINE and PIOGLITAZONE may result in reduced nimodipine plasma concentrations and lack of nimodipine efficacy.
Pioglitazone [Systemic] -- Tipranavir [Systemic]	**Moderate**	Concurrent use of PIOGLITAZONE and TIPRANAVIR may result in altered pioglitazone exposure or loss of glycemic control.
Trimethoprim [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of PIOGLITAZONE and TRIMETHOPRIM may result in increased pioglitazone exposure.
Pioglitazone -- Leflunomide And Metabolites **Pioglitazone Hydrochloride Interact(S) With:Interacting Substances**	**Moderate**	Concurrent use of PIOGLITAZONE and LEFLUNOMIDE AND METABOLITES may result in increased pioglitazone exposure.
Clarithromycin [Systemic] -- Pioglitazone [Systemic]	**Moderate**	Concurrent use of CLARITHROMYCIN and PIOGLITAZONE may result in increased exposure to pioglitazone.
MIDAZOLAM [Oral (Systemic)] -- PIOGLITAZONE [Oral (Systemic)]	**Moderate**	Concurrent use of PIOGLITAZONE and MIDAZOLAM may result in decreased plasma concentrations of midazolam.
Ginseng -- Antidiabetic Agents	**Moderate**	Concurrent use of GINSENG and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Pioglitazone -- Strong Cyp2c8 Inhibitors	**Moderate**	Concurrent use of PIOGLITAZONE and STRONG CYP2C8 INHIBITORS may result in increased pioglitazone plasma concentrations.

Pioglitazone Hydrochloride Interact(S) With:Interacting Substances		
Ace Inhibitors -- Antidiabetic Agents	**Moderate**	Concurrent use of ACE INHIBITORS and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Pioglitazone Hydrochloride Interact(S) With:Interacting Substances		
Glucosamine -- Antidiabetic Agents	**Minor**	Concurrent use of GLUCOSAMINE and ANTIDIABETIC AGENTS may result in reduced antidiabetic agent effectiveness.

Sitagliptin

Drugs:	Severity:	Summary:
Antidiabetic Agents -- Somatostatin Analogues **Sitagliptin Phosphate Interact(S) With: Interacting Substances**	**Major**	Concurrent use of ANTIDIABETIC AGENTS and SOMATOSTATIN ANALOGUES may result in impaired glucose regulation.
Chloroquine -- Antidiabetic Agents	**Major**	Concurrent use of CHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Sitagliptin -- Insulin Secretagogues **Sitagliptin Phosphate Interact(S) With: Interacting Substances**	**Major**	Concurrent use of SITAGLIPTIN and INSULIN SECRETAGOGUES may result in increased risk of hypoglycemia.
Fluoroquinolones -- Antidiabetic Agents **Sitagliptin Phosphate Interact(S) With: Interacting Substances**	**Major**	Concurrent use of FLUOROQUINOLONES and ANTIDIABETIC AGENTS may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.
Hydroxychloroquine -- Antidiabetic Agents	**Major**	Concurrent use of HYDROXYCHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Thioctic Acid -- Antidiabetic Agents	**Major**	Concurrent use of THIOCTIC ACID and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Simeprevir -- P-Glycoprotein Substrates	**Major**	Concurrent use of SIMEPREVIR and P-GLYCOPROTEIN SUBSTRATES may result in increased exposure of P-glycoprotein substrate.
Antidiabetic Agents -- Beta-Adrenergic Blockers **Sitagliptin Phosphate Interact(S) With: Interacting Substances**	**Moderate**	Concurrent use of ANTIDIABETIC AGENTS and BETA-ADRENERGIC BLOCKERS may result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.
Insulin Or Pramlintide -- Oral Antidiabetic Agents **Sitagliptin Phosphate Interact(S) With: Interacting Substances**	**Moderate**	Concurrent use of INSULIN OR PRAMLINTIDE and ORAL ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Antidiabetic Agents -- Selected Diuretics **Sitagliptin Phosphate Interact(S) With: Interacting Substances**	**Moderate**	Concurrent use of ANTIDIABETIC AGENTS and SELECTED DIURETICS may result in increased hyperglycemia risk; increased insulin requirement.

Ace Inhibitors -- Antidiabetic Agents Sitagliptin Phosphate Interact(S) With: Interacting Substances	Moderate	Concurrent use of ACE INHIBITORS and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Digoxin [Systemic] -- Sitagliptin [Systemic]	Minor	Concurrent use of DIGOXIN and SITAGLIPTIN may result in increased digoxin exposure and plasma concentration.

Dulaglutide

Drugs:	Severity:	Summary:
Dulaglutide -- Selected Sulfonylureas Dulaglutide Interact(S) With:Interacting Substances	Major	Concurrent use of DULAGLUTIDE and SELECTED SULFONYLUREAS may result in increased risk of hypoglycemia.
ANTIDIABETIC AGENTS -- SOMATOSTATIN ANALOGUES Dulaglutide Interact(S) With:Interacting Substances	Major	Concurrent use of ANTIDIABETIC AGENTS and SOMATOSTATIN ANALOGUES may result in impaired glucose regulation.
Chloroquine -- Antidiabetic Agents	Major	Concurrent use of CHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Hydroxychloroquine -- Antidiabetic Agents	Major	Concurrent use of HYDROXYCHLOROQUINE and ANTIDIABETIC AGENTS may result in hypoglycemia.
Thioctic Acid -- Antidiabetic Agents	Major	Concurrent use of THIOCTIC ACID and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
GLP-1 RECEPTOR AGONISTS -- INSULINS Dulaglutide Interact(S) With: Interacting Substances	Moderate	Concurrent use of GLP-1 RECEPTOR AGONISTS and INSULINS may result in increased risk of hypoglycemia.
ANTIDIABETIC AGENTS -- BETA-ADRENERGIC BLOCKERS Dulaglutide Interact(S) With: Interacting Substances	Moderate	Concurrent use of ANTIDIABETIC AGENTS and BETA-ADRENERGIC BLOCKERS may result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.
ANTIDIABETIC AGENTS -- SELECTED DIURETICS Dulaglutide Interact(S) With: Interacting Substances	Moderate	Concurrent use of ANTIDIABETIC AGENTS and SELECTED DIURETICS may result in increased hyperglycemia risk; increased insulin requirement.
ACE INHIBITORS -- ANTIDIABETIC AGENTS Dulaglutide Interact(S) With: Interacting Substances	Moderate	Concurrent use of ACE INHIBITORS and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.

Empagliflozin

Drugs:	Severity:	Summary:
Antidiabetic Agents -- Somatostatin Analogues Empagliflozin Interact(S) With: Interacting Substances	Major	Concurrent Use Of ANTIDIABETIC AGENTS And SOMATOSTATIN ANALOGUES May Result In Impaired Glucose Regulation.

Chloroquine -- Antidiabetic Agents	Major	Concurrent Use Of CHLOROQUINE And ANTIDIABETIC AGENTS May Result In Hypoglycemia.
Hydroxychloroquine -- Antidiabetic Agents	Major	Concurrent Use Of HYDROXYCHLOROQUINE And ANTIDIABETIC AGENTS May Result In Hypoglycemia.
Thioctic Acid -- Antidiabetic Agents	Major	Concurrent Use Of THIOCTIC ACID And ANTIDIABETIC AGENTS May Result In Increased Risk Of Hypoglycemia.
Antidiabetic Agents -- Beta-Adrenergic Blockers Empagliflozin Interact(S) With: Interacting Substances	Moderate	Concurrent Use Of ANTIDIABETIC AGENTS And BETA-ADRENERGIC BLOCKERS May Result In Hypoglycemia Or Hyperglycemia; Decreased Symptoms Of Hypoglycemia.
Insulin Or Pramlintide -- Oral Antidiabetic Agents Empagliflozin Interact(S) With: Interacting Substances	Moderate	Concurrent Use Of INSULIN OR PRAMLINTIDE And ORAL ANTIDIABETIC AGENTS May Result In Increased Risk Of Hypoglycemia.
Antidiabetic Agents -- Selected Diuretics Empagliflozin Interact(S) With: Interacting Substances	Moderate	Concurrent Use Of ANTIDIABETIC AGENTS And SELECTED DIURETICS May Result In Increased Hyperglycemia Risk; Increased Insulin Requirement.
Empagliflozin -- Insulin Secretagogues Empagliflozin Interact(S) With: Interacting Substances	Moderate	Concurrent Use Of EMPAGLIFLOZIN And INSULIN SECRETAGOGUES May Result In Increased Risk Of Hypoglycemia.
Ace Inhibitors -- Antidiabetic Agents Empagliflozin Interact(S) With: Interacting Substances	Moderate	Concurrent Use Of ACE INHIBITORS And ANTIDIABETIC AGENTS May Result In Increased Risk Of Hypoglycemia.

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Ministry of Health

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