Institut national d'excellence en santé et en services sociaux
Québec

QUEBEC'S NATIONAL MEDICAL PROTOCOL

No. 628004

Adjusting antidiabetic medication in type 2 diabetes

Developed in collaboration with an advisory committee consisting of Québec clinicians and experts.

CLINICAL SITUATION OR TARGET POPULATION

Person 18 years of age or older on antidiabetic therapy after having been diagnosed with type 2 diabetes.

CONTRAINDICATIONS TO APPLYING THIS PROTOCOL

- Type 1 diabetes
- Gestational diabetes
- Pregnancy or breastfeeding in a woman with type 2 diabetes
- Hospitalization for acute care, or acute phase of ketoacidosis or a hyperosmolar hyperglycemic syndrome

INSTRUCTIONS

GENERAL INFORMATION CONCERNING TREATMENT

Taking, right from diagnosis, measures by way of adopting healthy life habits and reinforcing and maintaining them over time is crucial to diabetes management.

Treatment with metformin monotherapy is usually prescribed if the glycated hemoglobin level (HbA_{1c}) at diagnosis exceeds the personal target by less than 1.5% and if the glycemic target is not achieved with lifestyle changes after 2 or 3 months.

Dual therapy combining metformin and another antidiabetic, chosen on the basis of the patient's clinical characteristics and the treatment priority (e.g., cardiovascular prevention, cardiorenal protection or weight management), is generally prescribed if the HbA_{1c} level at diagnosis exceeds the personal target by 1.5% or more and if the patient is asymptomatic. The table in Appendix III shows the differential characteristics and the details regarding the different classes of antidiabetics available in Canada.

- *The choice of antidiabetic prescribed for dual therapy should be based on an informed discussion covering the agent's benefits and drawbacks and take into account the patient's values and preferences and their ability to pay, based on their drug insurance coverage.*

Insulin therapy with or without metformin is generally prescribed in the presence of any of the following:

- *Symptomatic hyperglycemia;*
- *Metabolic decompensation (e.g., ketosis or unintentional weight loss);*
- *The need to quickly control the patient's blood glucose level when gradually introducing other antidiabetics.*

1. HEALTH STATUS ASSESSMENT WHEN MAKING THE ADJUSTMENT

1.1 Life habits

- Reinforce the adoption of healthy life habits during each visit for monitoring the antidiabetic medication and ask about the most recent changes made to their:
  - Eating habits, including the adoption of a new diet (e.g., ketogenic or intermittent fasting) and undernutrition;
  - Level of physical activity;
  - Smoking status, vaping habits or cannabis use;
  - Alcohol consumption.

! *The optimization of a healthy diet, physical activity or smoking cessation can take several weeks or months and be done in collaboration with different health professionals, including nurses, pharmacists, nutritionists and physical activity specialists.*

1.2 Health history and medication history

- ► Check the recent laboratory test results and the available capillary or interstitial glucose results;
- ► Check compliance and persistence with the prescribed antidiabetics;
- ► Inquire about any other change or factor that could influence the blood glucose or HbA_{1c} values, especially if there is a discrepancy between the two, including the use of new drugs or natural products (see list of factors in Appendix II);
- ► Ask about the latest changes that could require an adjustment to the prescribed antidiabetic medication, a substitution, a reevaluation of the antidiabetic therapy or a special follow-up:
  - Intolerable adverse effects;
  - Hypoglycemia symptoms (see Appendix I);
  - Signs and symptoms of hyperglycemia (see Appendix I);
  - Recent diagnosis of:
    - Heart failure (HF) or atherosclerotic cardiovascular disease (ASCVD) (e.g., a myocardial infarction, an ischemic stroke, unstable angina, or myocardial ischemia on imaging or a stress test);
    - Peripheral arterial or venous disease, or the occurrence of critical lower-limb ischemia;
    - Kidney or liver failure, whether acute or chronic.
  - A recent coronary, peripheral or carotid artery revascularisation procedure;
  - A recent diagnosis of, or the use of new medications for the management of, hypertension, dyslipidemia or familial hypercholesterolemia;
  - Rapid or unintentional weight gain or loss ≥ 5%;
  - The occurrence of symptoms associated with a complication of diabetes (e.g., retinopathy, neuropathy or diabetic foot);
  - Bariatric surgery within the past 6 months;
  - Recent hospitalization, fragility, a loss of autonomy, the appearance of neurocognitive issues, worsening health or reduced life expectancy;
  - Situation or personal preferences (e.g., burdensome treatment, or medication too expensive or not covered by the insurance plan).

1.3 Physical examination and vital signs

- ► Check the values of the previous measurements and then measure and record the following:
  - Body mass index
    - Waist
    - Weight
  - Blood pressure
  - Heart rate

- Check that the following elements for monitoring the diabetic patient's health have been examined within at least the past year or look for signs that might require a reevaluation, depending on the prescribed antidiabetic medication, and for the presence of diabetes complications, renal or cardiovascular comorbidities, or associated risk factors:
  - Diabetic foot (e.g., skin, nails, bone deformity, pedal pulse, cold foot and monofilament sensitivity test)
  - Lower limbs (e.g., the presence of pitting edema, intermittent claudication or a venous or arterial ulcer)
  - Optic fundus (e.g., impaired vision)
  - Oxygen saturation (e.g., dyspnea)
  - Unintentional weight gain or loss ≥ 5%

2. LABORATORY TESTS IN THE CONTEXT OF ANTIDIABETIC MEDICATION ADJUSTMENTS

- Fill out the appropriate request for the following laboratory tests for monitoring the adjustment of the different classes of antidiabetic drugs (with the exception of tests already done within the indicated timeframes).

! *For the **vitamin B_{12}** measurement, state the reasons for this request. Otherwise, the laboratory might refuse it.*
*The long-term use of metformin may be associated with vitamin B_{12} deficiency because of suboptimal absorption. A **vitamin B_{12}** measurement is also indicated in the presence of anemia or peripheral neuropathy.*

LABORATORY TESTS IN THE CONTEXT OF ANTIDIABETIC MEDICATION ADJUSTMENTS					
Test	**Before the start of pharmacological treatment[1]**	**Every 3 months**	**Every 6 months**	**Once a year**	**Once every 5 years**
All classes of antidiabetics, including insulin					
HbA_{1c}	√	√ [2]	√ [3]		
Serum creatinine (eGFR)[4]	√		√		
Urine ACR	√			√	
Lipid profile					√
Biguanides					
! Vitamin B_{12}				√ [5]	
Alpha-glucosidase inhibitors and thiazolidinediones					
ALT	√		√		
Oral semaglutide + Levothyroxine					
TSH	Monitoring may be necessary after introducing oral semaglutide.				

[1] A test performed during the 3 months prior to treatment is acceptable. These tests have normally been requested by prescribers and do not have to do with the adjustment of antidiabetic medications.

[2] When the capillary or interstitial glucose and HbA_{1c} targets have still not been achieved.

[3] When the capillary or interstitial glucose and HbA_{1c} targets are achieved.

[4] More frequent monitoring of renal function is generally useful in patients with high proteinuria (urine protein/creatine ratio > 30 mg/mmol, confirmed chronic renal failure, or a risk of acute renal failure).

[5] Vitamin B_{12} may be measured more frequently in the presence of new-onset anemia or if the patient has been diagnosed with peripheral neuropathy.

Abbreviations: ACR: urine albumin/creatinine ratio; ALT: alanine aminotransferase; CBC: complete blood count; HbA_{1c}: glycated hemoglobin; TSH: thyroid stimulating hormone.

Legend: √ Recommended √ Consider based on clinical judgment

3. GLYCEMIC TARGETS

- Individualize glycemic targets according to patient-specific clinical factors, such as the presence of cardiovascular disease and comorbidities, their life expectancy, the expected benefits compared to the risk of hypoglycemia, to weight gain and the other adverse effects, and, lastly, according to their values and preferences.
- Reevaluate glycemic targets on a regular basis to ensure that they are still appropriate.

GLYCATED HEMOGLOBIN AND CAPILLARY OR INTERSTITIAL GLUCOSE TARGETS			
Details	**Glycated hemoglobin (HbA_{1c}) (%)**	**Preprandial (AC) blood glucose; fasting (mmol/L)**	**2-h postprandial (PC) blood glucose (mmol/L)**
For most people with diabetes, the usual target for minimizing the risk of retinopathy, nephropathy and neuropathy	≤ 7.0	4.0 to 7.0[1]	5.0 to 10.0[1]
Life expectancy of at least 10 to 15 years; recent diagnosis; no significant cardiovascular disease, and use of antidiabetics with a low risk of hypoglycemia (to minimize the risk of nephropathy)	≤ 6.5	4.0 to 7.0[1]	5.0 to 10.0[1]
History of severe or unnoticed hypoglycemic episodes; or the presence of advanced micro- or macrovascular complications; or multiple comorbidities; or reduced life expectancy (< 10 years); or difficult-to-control longstanding diabetes; or fragile elderly person; or person with reduced autonomy	7.1 to 8.5	5.0 to 10.0[2]	6.0 to 14.0[2]
End of life	No target. Treat to minimize the symptoms of hypo- or hyperglycemia.		

[1] When the HbA_{1c} target is not achieved, aim for a preprandial blood glucose between 4.0 and 5.5 mmol/L and a postprandial blood glucose between 5.0 and 8.0 mmol/L.

[2] Or based on clinical judgment.

Blood glucose monitoring

- *Capillary blood glucose or interstitial fluid glucose measurement is a complement to the glycated hemoglobin measurement.*
- *To meet the Régie de l'assurance maladie du Québec (RAMQ)'s coverage conditions for test strips, the recommended blood glucose measurement times and frequency should be individualized according to the prescribed treatment, the risk of hypoglycemia, whether or not the targets are achieved, the information sought on the blood glucose level, and the possibility of changing a behaviour or the medication in light of the results. (Consult INESSS's optimal use guide on blood glucose monitoring in adults with type 2 diabetes not treated with insulin.). A reason code is used to obtain coverage for extra strips after clinical justification is provided to the pharmacist by the health professional who is providing the follow-up*
- *For certain patients, the use of a flash glucose monitoring system or a continuous monitoring device may be indicated over the use of a conventional glucometer.*
- *When adjusting a drug, consider the capillary or interstitial glucose levels for the past 3 to 7 days.*

4. TREATMENT APPROACH FOR ADJUSTMENTS

Based on the information gathered during the different steps of the health status assessment and on the clinician's judgment,

- Adjust the doses of the prescribed antidiabetic and assess the advisability of adding, discontinuing or substituting an antidiabetic, as needed:

Clinical situation	Therapeutic approach to be considered, based on the clinical picture and the clinician's judgment				
	Reevaluate the appropriateness of the treatment		Substitution by a prescriber	Increase dose	Add an antidiabetic for dual or triple therapy
	Reduce dose	Discontinue an antidiabetic			
HbA_{1c} level regularly below 6.5% or constantly lower than the personal target, if there is a risk of hypoglycemia	x	x	x		
Symptoms of hypoglycemia	x	x	x		
Intolerable adverse effects	x		x		
Decreased compliance and persistence with the prescribed antidiabetic medication			x		
Symptoms and signs of hyperglycemia				x	x
Appearance of symptoms associated with a complication of diabetes (e.g., retinopathy, neuropathy or diabetic foot)				x	x Consider a drug with cardiovascular protection
Recent diagnosis of MI or ASCVD			x Consider a drug with cardiovascular protection		x Consider a drug with cardiovascular protection
Recent coronary, peripheral or carotid artery revascularization procedure					
Recent diagnosis of, or the use of new medications for the management of, hypertension, dyslipidemia or familial hypercholesterolemia					
Recent diagnosis of liver failure	x		x		
Recent diagnosis or progression of chronic renal failure with an eGFR < 60 ml/min/1.73 m^2 or an ACR > 2 mg/mmol	x		x Consider a drug with renal protection		x Consider a drug with renal protection
Weight gain of 5% or more			x Consider a drug for weight control		x Consider a drug for weight control
Rapid or unintentional weight loss due to metabolic decompensation			x Consider an insulin		x Consider an insulin
Bariatric surgery within the past 6 months	x	x	x		
Frequent hospitalizations, worsening health, fragility, a loss of autonomy, the appearance of neurocognitive issues or reduced life expectancy	x	x	x		

General principles for adjusting antidiabetic medications

- All medication additions and adjustments, combined with lifestyle management, are aimed at achieving the targets within 3 to 6 months.
- The diet and antidiabetic doses need to be adjusted in order achieve the glycemic targets, but hypoglycemic episodes should be avoided and weight gain minimized.
- In general, it is preferable to increase the dose of only one agent at a time.
- When using insulin in combination with an oral or injectable antidiabetic and when an upward adjustment is necessary, choose the antidiabetic with a low risk of hypoglycemia. For a downward adjustment, choose the antidiabetic with a higher risk of hypoglycemia.

Principles concerning oral and injectable antidiabetics

- In general, all antidiabetics should be introduced at their starting doses, which can then be gradually increased, this to avoid hypoglycemic episodes and adverse effects (see the tables in Section 5 for details).
- When making the adjustment, return to the previous adjustment level if intolerance or hypoglycemic episodes occur.
- Combining antidiabetic at submaximal doses helps achieve glycemic targets faster with, possibly, fewer adverse effects than monotherapy at the maximum dose. However, in the case where the cardiovascular or renal benefits of certain antidiabetics are sought, one should aim to use doses for which such protection has been demonstrated (if they are tolerated).
- The choice of antidiabetic to be added is based on patient-specific clinical considerations, with priority given to cardiovascular and renal protection (see Appendix III) and on its mechanism of action (should be different from that of the antidiabetics currently being administered).
- When the personal HbA_{1c} target is already being achieved with dual or multiple therapy and an antidiabetic agent is added for its cardiorenal effects, it may be necessary to stop, or reduce the doses of, the antidiabetics that the patient is currently taking:
  - Deal with those that can cause hypoglycemic episodes first[1] (i.e., the secretagogues and insulin);
  - Discontinue DPP-4is if a GLP-1 receptor agonist is introduced.

Principles concerning insulin

- When insulin is added to the pharmacological treatment plan, it is preferable to start with a daily basal insulin to normalize the fasting blood glucose level.
- If the HbA_{1c} targets are still not achieved, multi-injection therapy (basal and prandial insulin) may be introduced gradually if a GLP-1 receptor agonist has already been optimized or cannot be added.
- When making the adjustment, hypoglycemic episodes should be corrected on a priority basis by decreasing the insulin responsible.

  Subsequently, the fasting hyperglycemic episodes can be corrected by adjusting the basal insulin, and the postprandial hyperglycemic episodes can be corrected by adjusting the prandial insulins.
- Do not take into account a hypoglycemic or hyperglycemic episode due to an explainable, exceptional, one-time situation (see Appendix II).

[1] Metformin should not be discontinued when multi-injection therapy is introduced, but sulfonylureas and meglitinides should be discontinued when two or more injections of prandial insulin are administered per day.

5. GENERAL INFORMATION ON ANTIDIABETICS AND ADJUSTMENT DETAILS

The general information on antidiabetics presented below is not exhaustive. The potential for drug interactions should be assessed whenever an addition or change is made to the medication profile.

A summary table of the different classes of antidiabetics, including additional information, such as their relative cost, their coverage by the RAMQ and their mechanism of action, is provided in Appendix III. The list of antidiabetics available in Canada is provided in Appendix IV.

The starting doses and adjustment frequencies indicated in the tables below are generally appropriate for elderly or fragile patients. In those cases where a dose or frequency range is given, it may be desirable to choose the lowest dose and to adjust the dosage at the lowest frequency in such patients.

5.1 Biguanides

GENERAL INFORMATION CONCERNING THE CLASS OF BIGUANIDES	
Contraindications	• A history of allergic reaction to biguanides • A history of lactic acidosis • Acute diabetic ketoacidosis • Severe renal failure: eGFR < 15 ml/min/1.73 m^2 • Severe liver failure • Severe respiratory failure and conditions associated with hypoxemia • Situations of stress: severe infection, trauma, or surgery
Precautions	• Renal failure: – eGFR 15-44 ml/min/1.73 m^2: exercise caution. Adjustment recommended. • Severe dehydration: may exacerbate renal failure • A contrast radiological examination, surgery (stop 48 hours before and resume 48 to 72 hours after, unless otherwise indicated by the medical team) • The presence of lactic acidosis risk factors for (acute or unstable heart failure, recent myocardial infarction, respiratory failure, dehydration [diarrhea, vomiting], alcohol abuse, renal failure, acute liver failure) • Decompensated heart failure • Pregnancy or breastfeeding
Most serious or frequent drug adverse effects	• Gastrointestinal disturbances (e.g., nausea, diarrhea and abdominal cramps) • Vitamin B_{12} deficiency • Lactic acidosis (rare)
Most significant drug interactions	• Drugs that can impair renal function in acute situations (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], antihypertensives in the class of angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs], diuretics, iodinated contrast agents, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors

DOSAGE TITRATION REGIMENS FOR THE CLASS OF BIGUANIDES				
Drug	**Starting dose and administration schedule**	**Maximum dose**	**Titration regimen**	**Adjustment if intolerance**
Metformin 500 and 850 mg scored tablets	250 to 500 mg PO BID at meals	2550 mg/day – eGFR[1] 30-44 ml/min/1.73 m^2: max. 1000 mg daily	↑ by 250 to 500 mg every 1 to 2 weeks or as tolerated The daily dose can be split into 2 or 3 doses (BID-TID), depending on tolerance and adherence.	↓ dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration: ↑ the dose by 250 mg (maximum 1 dose/day) or ↑ the adjustment interval[2].
Long-acting metformin 500 and 1000 mg unscored tablets	500 to 1000 mg PO daily (at dinner)	2000 mg/day – eGFR 30-44 ml/min/1.73 m^2: max. 1000 mg/day	↑ dose by 500 mg every 1 to 2 weeks	↓ dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration by increasing the adjustment interval.

[1] 500 mg daily administered in patients with an eGFR of 15-29 mL/min/1.73 m^2 in special situations, based on data from pharmacokinetic and non-clinical studies

[2] Extended-release metformin may be considered in patients with gastrointestinal intolerance to the regular form.

Abbreviation: eGFR: estimated glomerular filtration rate.

5.2 Secretagogues: sulfonylureas

GENERAL INFORMATION CONCERNING THE CLASS OF SECRETAGOGUES: SULFONYLUREAS	
Contraindications	• History of allergic reaction to sulfonylureas • Acute diabetic ketoacidosis • Severe liver failure • Renal failure: – Gliclazide, glimepiride: eGFR < 15 ml/min/1.73 m^2 – Glyburide: eGFR < 30 ml/min/1.73 m^2 • Situations of stress: severe infection, trauma, or surgery
Precautions	• History of allergic reaction to sulfonamides • Renal failure (↑ risk of hypoglycemic episodes): – Gliclazide, glimepiride: eGFR 15-29 ml/min/1.73 m^2 – Glyburide: eGFR 30-59 ml/min/1.73 m^2. Ideally, use another agent (↑ risk of hypoglycemic episodes) • Elderly patient, malnutrition, hepatic or renal failure, intense or prolonged exercise, alcohol consumption, especially in the fasting state (↑ risk of hypoglycemic episodes) • G6PD deficiency (↑ risk of hemolytic anemia) • Pregnancy or breastfeeding
Most frequent drug adverse effects	• Weight gain • Frequent hypoglycemic episodes (especially with glyburide)
Most significant drug interactions	• Under the influence of sympatholytic drugs (e.g., β-blockers and clonidine), symptoms of hypoglycemia may be ↓ or absent. • Concomitant use of other antidiabetics: risk of hypoglycemic episodes (a ↓ in the secretagogue dose may be required)

DOSAGE TITRATION REGIMENS FOR THE CLASS OF SECRETAGOGUES: SULFONYLUREAS				
Drug	**Starting dose and administration schedule**	**Maximum dose**	**Titration regimen**	**Adjustment if intolerance or hypoglycemia**
Gliclazide 80 mg scored tablets	40 to 80 mg PO BID with meals. If daily dose is ≥ 160 mg, administer the drug in 2 doses (BID)	320 mg/day	↑ each dose by 40 to 80 mg every 1 to 2 weeks	↓ dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration or ↑ adjustment interval.
Gliclazide (extended release) 30 mg (unscored) and 60 mg (scored) tablets	30 mg PO daily at breakfast OR at the first main meal of the day	120 mg/day	↑ the dose by 30 mg every 1 to 2 weeks	
Glimepiride 1, 2 and 4 mg tablets	0.5 to 1 mg PO daily at breakfast OR at the first main meal of the day	8 mg/day	↑ the dose by 0.5 to 1 mg every 1 to 2 weeks	
Glyburide 2.5 and 5 mg scored tablets	1.25 to 5 mg PO daily at meals (in 1 or 2 doses daily or BID). If administered daily, give at the first main meal of the day	20 mg/day (max. 10 mg per dose)	↑ each dose by 1.25 to 2.5 mg every 1 to 2 weeks The daily dose can be split into 2 doses (BID) if the AC capillary or interstitial glucose levels at breakfast remain > 7 mmol/L	

Abbreviations: eGFR: estimated glomerular filtration rate; G6PD: glucose-6-phosphate dehydrogenase.

5.3 Secretagogues-meglitinides

GENERAL INFORMATION CONCERNING THE CLASS OF SECRETAGOGUES: MEGLITINIDES	
Contraindications	• History of allergic reaction to meglitinides • Acute diabetic ketoacidosis • Liver failure • The use of gemfibrozil or clopidogrel[1] • Pregnancy or breastfeeding
Precautions	• Do not take repaglinide if meal is skipped; delay repaglinide if meal is delayed. • Elderly patient, malnutrition, hepatic or renal failure, intense or prolonged exercise, alcohol intake, especially in the fasting state (↑ the risk of hypoglycemic episodes)
Most frequent drug adverse effects	• Hypoglycemic episodes • Weight gain • Headache
Most significant drug interactions	• CYP3A4 and/or CYP2C8 inhibitors (e.g., gemfibrozil, clopidogrel[1], clarithromycin, ketoconazole, cyclosporine and trimethoprim): ↑ plasma repaglinide concentration (↑ risk of hypoglycemic episodes). • Concomitant use of other antidiabetics: risk of hypoglycemic episodes (a ↓ in the secretagogue dose may be required)

[1] Clopidogrel is contraindicated with repaglinide because it can increase its active concentration and thereby increase the risk of hypoglycemic episodes. In practice, repaglinide can be used with caution, using the lowest possible doses and ensuring that no hypoglycemic episodes occur.

DOSAGE TITRATION REGIMENS FOR THE CLASS OF SECRETAGOGUES: MEGLITINIDES				
Drug	**Starting dose and administration schedule**	**Maximum dose**	**Titration regimen**	**Adjustment if intolerance or hypoglycemia**
Repaglinide 0.5, 1 and 2 mg tablets	0.5 to 1 mg per meal PO daily, BID or TID 0-15 minutes before meal	12 mg/day (max. 4 mg per dose) – eGFR < 30 ml/min/1.73 m^2: start with lowest dose	If average mealtime capillary blood glucose level is high (> 7 mmol/L or > target set by the prescriber), double the dose that was given at the previous meal Adjustment interval: every week The daily dose can be split into 3 doses (TID)	↓ dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration or ↑ adjustment interval.

5.4 Glucagon-like peptide (GLP-1) receptor agonists

GENERAL INFORMATION CONCERNING THE CLASS OF GLP-1 RECEPTOR AGONISTS	

Contraindications	• History of allergic reaction to GLP-1s
	• Acute diabetic ketoacidosis
	• Pregnancy or breastfeeding
	• A personal or family history of medullary thyroid carcinoma
	• Multiple endocrine neoplasia syndrome type 2
	• Renal failure:
	  - Exenatide: eGFR < 30 ml/min/1.73 m^2
	  - Liraglutide, lixisenatide, semaglutide: eGFR < 15 ml/min/1.73 m^2

Precautions	• Renal failure:
	  - eGFR < 50 ml/min/1.73 m^2: adjust cautiously to avoid nausea/vomiting, which can cause dehydration, and monitor renal function more closely in the presence of severe or acute gastrointestinal symptoms that can cause dehydration
	  - Dulaglutide: eGFR < 15 ml/min/1.73 m^2: exercise caution (limited data)
	  - Semaglutide, lixisenatide: eGFR between 15 and 29 ml/min/1.73 m^2: exercise caution (limited data)
	• Liver failure
	• History of or risk factors for pancreatitis (biliary lithiasis, alcoholism, hypertriglyceridemia): discontinue if symptoms of pancreatitis
	• Semaglutide[1]: ↑ the rate of diabetic retinopathy complications in individuals with a history of retinopathy
	• Heart diseases that can be exacerbated by an ↑ in the heart rate or by a PR interval prolongation (e.g., congestive heart failure, atrial fibrillation, tachyarrhythmia, or 1st-degree (pronounced) or 2nd- or 3rd-degree atrioventricular block)
	• Gastroparesis

Most frequent drug adverse effects	• Gastrointestinal disturbances (e.g., nausea, vomiting and diarrhea: ↓ in effects after a few weeks) • ↑ heart rate (2 to 4 beats/minute) • Injection site reaction (SC GLP-1s)
Most significant drug interactions	• Insulins and secretagogues: risk of hypoglycemic episodes (a ↓ in the insulin or secretagogue dose may be required) • Short-acting GLP-1s (short-acting exenatide, lixisenatide): take oral medications (e.g., antibiotics) at least 1 hour before or 4 hours after (as absorption may be delayed) • Oral GLP-1s: take 30 minutes before meals and 30 minutes before other oral medications (GLP-1s can slow the absorption of other oral medications) • Warfarin (if exenatide): possible ↑ in the INR • Drugs that can prolong the PR interval (e.g., antiarrhythmics, nondihydropyridine calcium channel blockers, β-blockers, digitalis glycosides, HIV protease inhibitors, and somatostatin analogues) • Drugs that ↑ the heart rate (e.g., sympathomimetics and anticholinergics) • Levothyroxine (if oral semaglutide taken concurrently): possible ↑ in thyroxine levels. Monitor thyroid parameters more closely

[1] In patients with a history of retinopathy or who have not been screened, an appropriate ophthalmic follow-up and a gradual increase in the semaglutide doses are recommended to prevent too rapid a decrease in the HbA_{1c} level.

Abbreviations: eGFR: estimated glomerular filtration rate; HIV: human immunodeficiency virus; INR: international normalized ratio; SC: subcutaneous.

DOSAGE TITRATION REGIMENS FOR THE CLASS OF GLP-1 RECEPTOR AGONISTS

	Drug	Starting dose and administration schedule	Maximum dose	Titration regimen	Adjustment if intolerance
Long-acting	**Dulaglutide** Prefilled single-dose injector pens with 0.75 mg/0.5 ml and 1.5 mg/0.5 ml	0.75 mg SC every week[1]	1.5 mg/week	↑ the dose by 0.75 mg SC after 4 weeks	↓ dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration or ↑ adjustment interval.
	Exenatide – extended release Prefilled single-dose injector pen containing 2 mg. Reconstituted with accompanying diluent.	2 mg SC every week[1]	2 mg/week	--	
	Liraglutide Prefilled multidose injector pen containing 6 mg/ml: 0.6 mg, 1.2 mg or 1.8 mg doses	0.6 mg[2] SC daily. If severe nausea, the dose can be taken at bedtime (HS).	1.8 mg/day	↑ the dose by 0.6 mg SC daily every 1 to 2 weeks	
	Semaglutide injectable[3] Prefilled multidose injector pens containing 1.34 mg/ml 1.5 ml pen: 0.25 mg or 0.5 mg doses 3 ml pen: 1 mg doses	0.25 mg[2] SC every week[4]	1 mg/week	↑ the dose to 0.5 mg SC after 4 weeks. If blood glucose levels are still not under control after 4 weeks with this adjustment, the dose can be ↑ to 1 mg	
	Oral semaglutide[3] 3 mg, 7 mg and 14 mg tablets	3 mg[2] PO every morning in the fasting state with a max. of 120 ml of water and at least 30 minutes before drinking, eating or taking any other oral medication[5]	14 mg/day	↑ the dose to 7 mg PO after 30 days. If blood glucose levels are still not under control after 30 days at this dose, the dose can be ↑ to 14 mg[6]	
Short-acting	**Exenatide** Prefilled multidose injector pens containing 250 mcg/ml: 1.2 ml pen: 5 mcg doses 2.4 ml pen: 10 mcg doses	5 mcg SC BID within 60 minutes before morning and evening meals (or the two main meals of the day, with the doses at least 6 hours apart)	20 mcg/day (max. 10 mcg per dose)	↑ to 10 mcg SC BID after 4 weeks of treatment	
	Lixisenatide Prefilled multidose injector pens 0.05 mg/ml pen: 10 mcg doses 0.1 mg/ml pen: 20 mcg doses	10 mcg SC daily within 60 minutes before a meal (same meal each day)	20 mcg/day	↑ to 20 mcg SC daily after 14 days	

[1] The administration schedule can be modified: observe a minimum of 72 hours between doses.

[2] Starting dose to mitigate gastrointestinal effects, but not sufficient for glycemic control.

[3] According to the U.S. product monograph, patients receiving 14 mg/day PO of semaglutide can be switched to 0.5 mg/week SC the day after their last dose of oral semaglutide. Those receiving 0.5 mg/week SC of semaglutide can be switched to 7 or 14 mg/day PO within 7 days after their last injection of semaglutide injectable. There is no oral semaglutide dose equivalent to 1 mg/week of semaglutide injectable.

[4] The administration schedule can be modified: observe a minimum of 48 hours between doses.

[5] Drastic loss of efficacy (oral absorption) if the patient is unable to follow this complex dosing regimen.

[6] Do not take more than one tablet per day. It is not recommended to take 2 tablets a day (e.g., two 7 mg tablets to obtain 14 mg of semaglutide) in order to meet the intended daily amount of salcaprozate sodium.

5.5 Sodium-glucose cotransporter-2 (SGLT-2) inhibitors

GENERAL INFORMATION CONCERNING THE CLASS OF SGLT-2IS	
Contraindications	• History of allergic reaction to SGLT-2is • Acute diabetic ketoacidosis • Pregnancy or breastfeeding • Dapagliflozin: active bladder cancer • Renal failure: - Dapagliflozin: do not introduce if eGFR < 25 ml/min/1.73 m^2 - Canagliflozin: if eGFR < 30 ml/min/1.73 m^2 - Empagliflozin: if eGFR < 20 ml/min/1.73 m^2
Precautions	• Renal failure[1]: monitor renal function more frequently if eGFR < 60 ml/min/1.73 m^2 • Dehydration: can impair renal function • Severe liver failure • Risk of diabetic ketoacidosis, even if euglycemia • Risk factors[2]: recent bariatric or other surgery, reduced carbohydrate intake (e.g., ketogenic diet), a period of fasting, alcohol, intense or prolonged exercise, insulin deficiency, dehydration, infection • Surgery, infection, dehydration, vomiting or diarrhea: stop (in advance when possible), then resume when patient's clinical status so permits • Elderly patients (risk of dehydration, hypotension, volume depletion) • Patients with critical lower-limb ischemia of a or non-reepithelialized ulcer: do not introduce, or discontinue until resolution • Dapagliflozin: history of bladder cancer • Empagliflozin: not recommended for glycemic control if eGFR < 30 ml/min/1.73 m^2 but can be continued at 10 mg daily for its cardiorenal benefits
Most frequent or serious drug adverse effects	• Hypotension • Genital yeast infection • Pollakiuria • Polyuria • Urinary tract infection • Diabetic ketoacidosis
Most significant drug interactions	• Digoxin (canagliflozin): ↑ in plasma digoxin level • Loop diuretics (especially furosemide): risk of volume depletion (a ↓ in the loop diuretic dose may be considered; monitor blood pressure closely) • Antihypertensives: risk of hypotension (a ↓ in the antihypertensive dose may be considered; monitor blood pressure closely) • Insulin and secretagogues: risk of hypoglycemic episodes (a ↓ in the insulin or secretagogue dose may be required)

[1] Dapagliflozin, canagliflozin, empagliflozin: weak hypoglycemic effect in patients with an eGFR < 45 ml/min/1.73 m^2, but cardiovascular and renal protection is maintained.
[2] List not exhaustive.

DOSAGE TITRATION REGIMENS FOR THE CLASS OF SGLT-2IS				
Drug	**Starting dose and administration schedule**	**Maximum dose**	**Titration regimen**	**Adjustment if intolerance**
Canagliflozin 100 and 300 mg tablets	100 or 300 mg PO daily in the morning	300 mg/day – eGFR between 30 and 59 ml/min/1.73 m^2: max. 100 mg/day	↑ the dose to 300 mg after 4 weeks (if eGFR > 60 ml/min/1.73 m^2)	↓ the dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration or ↑ adjustment interval.
Dapagliflozin 5 and 10 mg tablets	5 or 10 mg PO daily in the morning	10 mg/day	↑ the dose to 10 mg after 4 weeks	
Empagliflozin 10 and 25 mg tablets	10 or 25 mg PO daily in the morning	25 mg/day – eGFR < 30 ml/min/1.73 m^2: max. 10 mg/day (for cardiorenal benefits only)	↑ the dose to 25 mg after 4 weeks	

Abbreviation: eGFR: estimated glomerular filtration rate.

5.6 Dipeptidyl peptidase-4 inhibitor (DPP-4is)

GENERAL INFORMATION CONCERNING THE CLASS OF DPP-4IS	
Contraindications	• History of allergic reaction to DPP-4 inhibitors • Acute diabetic ketoacidosis • Pregnancy or breastfeeding
Precautions	• Renal failure: – Linagliptin: if eGFR < 15 ml/min/1.73 m^2 – Saxagliptin: if eGFR < 15 ml/min/1.73 m^2 • Moderate to severe liver failure • Pancreatitis • Saxagliptin: patients with a history of heart failure
Most frequent or serious drug adverse effects	• Headache • Nasopharyngitis, upper respiratory tract infection • Pancreatitis (rare) • Joint pain (rare; mostly with saxagliptin)
Most significant drug interactions	• Insulin and secretagogues: risk of hypoglycemic episodes (a ↓ in the insulin or secretagogue dose may be necessary) • CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin and protease inhibitors): possible increase in the effect of saxagliptin

TITRATION REGIMENS FOR THE CLASS OF DPP-4IS			
Drug	**Starting dose**	**Maximum dose**	**Adjustment according to renal function**
Alogliptin 6.25, 12.5 and 25 mg tablets	25 mg PO daily	25 mg/day	• eGFR between 30 and 59 ml/min/1.73 m^2: 12.5 mg PO daily • eGFR < 30 ml/min/1.73 m^2: 6.25 mg PO daily
Linagliptin 5 mg tablets	5 mg PO daily	5 mg/day	No adjustment necessary[1]
Saxagliptin 2.5 and 5 mg tablets	5 mg PO daily	5 mg/day	• eGFR < 45 ml/min/1.73 m^2: 2.5 mg PO daily
Sitagliptin 25, 50 and 100 mg tablets	100 mg PO daily	100 mg/day	• eGFR between 30 and 44 ml/min/1.73 m^2: 50 mg PO daily • eGFR < 30 ml/min/1.73 m^2: 25 mg PO daily

[1] Little data is available for when the eGFR is < 15 ml/min/1.73 m^2. Exercise caution.

Abbreviation: eGFR: estimated glomerular filtration rate.

5.7 Thiazolidinediones (TZDs)

GENERAL INFORMATION CONCERNING THE CLASS OF THIAZOLIDINEDIONES (TZDS)	
Contraindications	• History of allergic reaction to thiazolidinediones • Acute diabetic ketoacidosis • Pregnancy or breastfeeding • Pioglitazone: bladder cancer (active or past) • Pioglitazone: uninvestigated hematuria • Heart failure (NYHA classes 1 to 4) or left ventricular dysfunction[1] • Severe liver failure
Precautions	• Renal failure: eGFR < 60 ml/min/1.73 m^2: exercise caution (may cause fluid retention) • Atherosclerotic cardiovascular disease (ASCVD) • Peripheral edema • Elderly patients: ↑ the incidence of edema and congestive heart failure • Osteoporosis • Macular edema • Perimenopause (may restore ovulation): ↑ the risk of pregnancy
Most frequent drug adverse effects	• Weight gain[1] • Heart failure[1] • Edema[1] • Bone fractures (ankles, wrists): especially in women during long-term use
Most significant drug interactions	• Insulin and other drugs that can increase fluid retention • CYP2C8 inhibitors (e.g., gemfibrozil): ↑ the plasma thiazolidinedione level

[1] Situation requiring special attention, further investigation or a reassessment: weight gain > 3 kg in 2 weeks and the presence of the following symptoms: lower-limb edema, dyspnea, unusual fatigue. Discontinue the drug.

DOSAGE TITRATION REGIMENS FOR THE CLASS OF THIAZOLIDINEDIONES (TZDS)				
Drug	**Starting dose and administration schedule**	**Maximum dose**	**Titration regimen**	**Adjustment if intolerance**
Pioglitazone 15, 30 and 45 mg tablets	15 mg PO daily in the morning	45 mg/day	↑ the dose by 15 mg every 8 to 12 weeks	↓ dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration or ↑ the adjustment interval.
Rosiglitazone[2] 2, 4 and 8 mg	4 mg/day PO in one or two doses (daily or BID)	8 mg/day If combined with a sulfonylurea: 4 mg/day	↑ the dose to 8 mg/day after 8 to 12 weeks	

[2] An informed consent form provided by the manufacturer accompanies prescriptions for rosiglitazone.

Abbreviation: eGFR: estimated glomerular filtration rate.

5.8 Alpha-glucosidase inhibitors

GENERAL INFORMATION CONCERNING THE CLASS OF ALPHA-GLUCOSIDASE INHIBITORS	
Contraindications	• History of allergic reaction to alpha-glucosidase inhibitors • Acute diabetic ketoacidosis • Pregnancy or breastfeeding • Inflammatory bowel disease • Intestinal obstruction • Cirrhosis • Colonic ulcer • Renal failure: eGFR < 25 ml/min/1.73 m^2
Precautions	• Chronic intestinal diseases: pronounced digestive or absorption disorders or conditions that can be exacerbated by increased intestinal gas production (e.g., large hernias and irritable bowel syndrome) • If hypoglycemia occurs, do not give sucrose (e.g., juice or white sugar). Give honey or milk instead.
Most frequent drug adverse effects	• Gastrointestinal disturbances (e.g., diarrhea, flatulence and bloating) • ↑ transaminases
Most significant drug interactions	• Digoxin: acarbose may ↓ digoxin absorption

DOSAGE TITRATION REGIMENS FOR THE CLASS OF ALPHA-GLUCOSIDASE INHIBITORS				
Drug	**Starting dose and administration schedule**	**Maximum dose**	**Titration regimen**	**Adjustment if intolerance**
Acarbose 50 and 100 mg scored tablets	25 to 50 mg PO daily, BID or TID at beginning of meal	300 mg/day	Depending on the postprandial glucose levels and tolerance, ↑ the dose very slowly from 25 mg for one meal at a time to 50 mg TID every 2 to 4 weeks The daily dose can be split into 3 doses (TID).	↓ dose to the lower adjustment level or attempt a temporary pause of 1 week or until symptom resolution. Resume at starting dose or lower tolerated level (if stopped). Resume with a slower titration or ↑ the adjustment interval.

Abbreviation: eGFR: estimated glomerular filtration rate.

5.9 Insulins

GENERAL INFORMATION CONCERNING INSULINS	
Contraindications	• A history of allergic reaction to the insulin formulation (rare; if present, switch to another type of insulin)
Precautions	• Pregnancy or breastfeeding: dose adjustments frequently required • Elderly patient, malnutrition, liver failure, renal failure, intense or prolonged exercise, alcohol use, especially in the fasting state (↑ risk of hypoglycemic episodes): close monitoring of blood glucose levels required
Most frequent drug adverse effects	• Frequent hypoglycemic episodes • Significant weight gain • Injection site reaction
Most significant drug interactions	• Thiazolidinediones: risk of heart failure • Under the influence of sympatholytic drugs (e.g., β-blockers and clonidine), symptoms of hypoglycemia may be milder or absent. • The concomitant use of other antidiabetic agents: risk of hypoglycemia (a ↓ in the insulin dose may be required)

STARTING DOSES FOR THE CLASS OF INSULINS[1]	
Basal insulin	4 to 10 units in a once-daily injection
Prandial insulin (one injection per day in addition to basal insulin)	2 to 4 units or 10% of the basal dose at the main meal or at breakfast.
Prandial insulin (several injections per day in addition to basal insulin):	Calculate the total daily dose of 0.3 to 0.5 units/kg and allot as follows: • 40% of total insulin as basal insulin • 20% of total insulin as a bolus 3 times a day with prandial insulin
No maximum dose	

[1] Examples of usually prescribed starting doses.

INSULINS							
Insulin	**Action**	**Type of insulin**	**Onset of action**	**Peak action**	**Duration of action**	**Usual time of administration**	**Blood glucose level for making adjustment**
BASAL	Intermediate-acting	Isophane (NPH)	1 to 3 hours	5 to 8 hours	Up to 18 hours	30 minutes before breakfast	AC dinner blood glucose level
						30 minutes before dinner	Next-day AC breakfast blood glucose level
						At bedtime	Next-day AC breakfast blood glucose level
	Long-acting analogues	Detemir	90 minutes	Not applicable	16 to 24 hours	At bedtime	Next-day AC breakfast blood glucose level
		Glargine	90 minutes	Not applicable	Up to 24 hours	At bedtime	Next-day AC breakfast blood glucose level
		Glargine 300 units/ml[1]	Up to 6 hours	Not applicable	More than 30 hours	At the same time every day	AC breakfast blood glucose level on following days
		Degludec[1]	2 hours	Not applicable	More than 42 hours	At the same time every day	AC breakfast blood glucose level on following days
PRANDIAL	Short-acting	Crystalline zinc (regular)	30 minutes	2 to 3 hours	6.5 hours	15 to 30 minutes before meal	AC next-meal blood glucose level
	Fast-acting analogues	Aspart	10 to 15 minutes	1 to 1.5 hours	3 to 5 hours	0 to 15 minutes before breakfast 0 to 15 minutes before lunch 0 to 15 minutes before dinner	Pre-breakfast dose: 2-hr PC breakfast blood glucose level or AC lunch blood glucose level[2] Pre-lunch dose: 2-hr PC lunch blood glucose level or AC dinner blood glucose level[2] Pre-dinner dose: 2-hr PC dinner blood glucose level or HS blood glucose level
		Glulisine	10 to 15 minutes	1 to 1.5 hours	3 to 5 hours		
		Lispro	10 to 15 minutes	1 to 2 hours	3,5 to 4.75 hours		
	Ultrafast-acting analogue	Rapid aspart	4 minutes	0.5 to 1.5 hours	3 to 5 hours	0 to 2 minutes AC to 20 minutes after the start of breakfast 0 to 2 minutes AC to 20 minutes after the start of lunch 0 to 2 minutes AC to 20 minutes after the start of dinner	
PRANDIAL-BASAL	Short/inter-mediate-acting (premixed)	Regular/NPH 30/70 40/60 50/50	Depends on prandial/basal ratio			15 to 30 minutes before breakfast 15 to 30 minutes before dinner	Pre-breakfast dose: AC lunch blood glucose level and AC dinner blood glucose level Pre-dinner dose: HS blood glucose level and next-day AC breakfast blood glucose level
	Short/inter-mediate-acting analogues (premixed)	Biphasic aspart Mix 30 Lispro/lispro protamine Mix 25 Mix 50	Depends on prandial/basal ratio			0 to 15 minutes before breakfast 0 to 15 minutes before dinner	Pre-breakfast dose: 2-hr PC breakfast blood glucose level or AC lunch blood glucose level[2] and AC dinner blood glucose level Pre-dinner dose: 2-hr PC dinner blood glucose level or HS blood glucose level[2] and next-day AC breakfast blood glucose level
	Fast- and long-acting	Crystalline zinc 500 units/ml[1]	15 minutes	4 to 8 hours	17 to 24 hours	30 minutes before breakfast 30 minutes before lunch 30 minutes before dinner	Pre-breakfast dose: AC lunch blood glucose level and AC dinner blood glucose level Pre-lunch dose: AC dinner blood glucose level and HS blood glucose level Pre-dinner dose: HS blood glucose level and next-day AC breakfast blood glucose level

[1] Concentrated insulins (200 units/ml, 300 units/ml and 500 units/ml) should never be transferred from the pre-filled pen to another device, such as a syringe. The graduations on an insulin syringe do not permit an accurate dose measurement. This increases the risk of severe hypoglycemia.

[2] If the blood glucose level is not measured 2 hours PC.

INSULIN TITRATION REGIMENS ADJUSTMENT INTERVAL: EVERY 3 TO 7 DAYS			
Time of day	**Capillary blood glucose result**[1]	**Adjustment**[2, 3, 4]	**Insulin responsible**
NIGHT, BREAKFAST	< 4 mmol/L or < glycemic targets	↓ insulin dose by 10% OR ↓ dose by 2 to 4 units	Adjust the basal insulin administered at dinner or bedtime or the prandial-basal insulin at dinner
	> 7 mmol/L or > glycemic targets and no nocturnal hypoglycemic episodes	↑ insulin dose by 10% OR ↑ dose by 1 to 2 units (↑ dose by 2 to 4 units if blood glucose ≥ 10 mmol/L)	
LUNCH	< 4 mmol/L or < glycemic targets	↓ insulin dose by 10% OR ↓ dose by 2 to 4 units	Adjust the prandial or prandial-basal insulin administered at breakfast
	> 7 mmol/L or > glycemic targets	↑ insulin dose by 10% OR ↑ dose by 1 to 2 units (↑ dose by 2 to 4 units if blood glucose ≥ 10 mmol/L)	
AFTERNOON (within 3 hours after lunch)	< 4 mmol/L or < glycemic targets	↓ insulin dose by 10% OR ↓ dose by 2 to 4 units	Adjust the prandial insulin administered at lunch
	> 7 mmol/L or > glycemic targets	↑ insulin dose by 10% OR ↑ dose by 1 to 2 units (↑ dose by 2 to 4 units if blood glucose ≥ 10 mmol/L)	
DINNER (more than 3 hours after lunch)	< 4 mmol/L or < glycemic targets	↓ insulin dose by 10% OR ↓ dose by 2 to 4 units	Adjust the basal or prandial-basal insulin administered at breakfast or the prandial or fast- and long-acting insulin (crystalline zinc 500 units/ml) administered at lunch
	> 7 mmol/L or > glycemic targets	↑ insulin dose by 10% OR ↑ dose by 1 to 2 units (↑ dose by 2 to 4 units if blood glucose ≥ 10 mmol/L)	
BEDTIME	< 4 mmol/L or < glycemic targets	↓ insulin dose by 10% OR ↓ dose by 2 to 4 units	Adjust the prandial or prandial-basal insulin administered at dinner or the fast- and long-acting insulin (crystalline zinc 500 units/ml) administered at lunch
	> 7 mmol/L or > glycemic targets	↑ insulin dose by 10% OR ↑ dose by 1 to 2 units (↑ dose by 2 to 4 units if blood glucose ≥ 10 mmol/L)	

[1] Calculate the average capillary or interstitial glucose levels for the past 3 to 7 days for each time of the day.

[2] Two ways to adjust insulin: a) the percentage of insulin dose OR b) the number of insulin units.

[3] Round off the dose (minimum 1 unit).

[4] Titration steps can be more than 4 units at a time if there is insulin resistance (total dose > 100 units per 24 hours).

6. INFORMATION TO BE PROVIDED

Discuss the following with the patient:

GENERAL CONSIDERATIONS
- The optimization of life habits (diet, alcohol/tobacco use, physical activity and weight loss), the impact on diabetes and overall health, and the resources available to help achieve this (referral, if possible); - Education on foot self-inspection and the importance of foot care; - The indication, dosing and schedule for administering prescribed antidiabetics; - Adverse effects (management and prevention); - The importance of compliance and persistence with the treatments (antidiabetics and non-antihyperglycemic cardiovascular drugs). If necessary, make the patient aware of the importance of continuously adhering to their medication in order to control both their diabetes and comorbidities in order to reduce their cardiovascular risk; - The procedure in the event of a missed or incorrect dose (see Appendix V); - The current glycemic values and therapeutic target; - Verification of blood glucose measurement technique. If necessary, provide technical support; - The importance of the patient recording, analyzing and interpreting their blood glucose results themselves; - The frequency of follow-up visits; - Preparation for the next follow-up visit: times and frequency of blood glucose self-monitoring and blood samples for laboratory tests; - Self-management of the treatment (insulin); - The number of test strips needed and the number covered by the RAMQ according to the antidiabetic treatment (if applicable).
PRECAUTIONS
- Symptoms of hypoglycemia and hyperglycemia; - The prevention and treatment of hypoglycemic episodes (e.g., during intense or prolonged exercise or physical work); - Action plan for days when sick (medications to be paused and increased hydration and self-monitoring); - Reasons for contacting the medical clinic or their doctor, or to go to the emergency room; - Risks associated with other drugs, prescription or over-the-counter, natural products or certain diets (e.g., ketogenic diet); - The importance of carrying a card or wearing a bracelet indicating the use of an antidiabetic (if applicable) - Driving: blood glucose self-monitoring required, strategies for reducing the risk of hypoglycemia (if applicable); - Pregnancy planning or the use of a method of contraception (if applicable).

7. FOLLOW-UP

Based on the information gathered during the health status assessment:

- ► Arrange for the next follow-up contact (e.g., a phone call or an appointment with the prescriber);
- ► Determine if laboratory tests need to be done and how soon;
- ► Specify the blood glucose measurements to be done for the purpose of the next follow-up contact.

8. SITUATIONS REQUIRING SPECIAL ATTENTION, A REASSESSMENT OR FURTHER INVESTIGATION

- ► Pronounced hyperglycemic episodes with or without symptoms or signs of ketoacidosis (see Appendix I);
- ► Unexplained hypoglycemic episodes that are recurrent or without warning signs;
- ► Glycemic targets not achieved after 6 months of treatment adjustments;
- ► Glycemic targets not achieved with the maximum prescribed dose indicated in this protocol or with the maximum tolerated dose;
- ► Recent emergency department visit or hospitalization;
- ► The occurrence of atherosclerotic cardiovascular disease (ASCVD) (e.g., a recent event or recent diagnosis of myocardial infarction, heart failure, ischemic stroke, unstable angina; coronary, carotid or peripheral artery revascularization procedure), peripheral arterial or venous disease (PAD or PVD), or symptoms and signs of progressing or confirmed ASCVD, PAD or PVD (e.g., toe amputation);
- ► The development of renal failure (eGFR < 60 ml/min/1.73 m^2 or ACR > 2 mg/mmol), a rapid or unexplained decline in renal function, or progression of confirmed chronic renal failure with an eGFR result below a precaution threshold for the prescribed medication or if the failure becomes severe (eGFR < 30 ml/min/1.73 m^2);
- ► Elevation of ALT to more than 2.5 times the upper limit of normal (ULN) (for thiazolidinediones and alpha-glucosidase inhibitors) or symptoms and signs of progression of confirmed liver failure or of severe liver failure;
- ► Vitamin B_{12} deficiency (for metformin);
- ► The development of symptoms or signs associated with a diabetic complication (e.g., retinopathy, neuropathy or diabetic foot);
- ► The presence of critical lower-limb ischemia or nonrepithelialized ulcer (for SGLT-2is);
- ► Rapid or unintentional weight gain or loss of 5% or more, depending on the individual's overall physical condition and their antidiabetic medication;
- ► Significant lifestyle changes or bariatric surgery with significant weight loss of at least 5% AND an HbA_{1c} below 6.0% or below the patient's target, or episodes of significant hypoglycemia;
- ► The emergence, during treatment, of a contraindication to applying this protocol or to the medication;
- ► Noncompliance with the medication regularly noted;
- ► Intolerance to the medication;
- ► Worsening health;
- ► The need for additional test strips, which involves providing clinical justification for RAMQ coverage (if applicable).

REFERENCES

This protocol is based on the latest scientific data and best clinical practice recommendations, which were supplemented with contextual information and the experiential knowledge of Québec clinicians and experts. For details on the process used to develop this national medical protocol and to consult the bibliographic references, see the supporting report.

APPENDIX I - SYMPTOMS OF HYPOGLYCEMIA AND HYPERGLYCEMIA AND WARNING SIGNS

- Typical symptoms of hypoglycemia[1]
- Tremor
- Palpitations (tachycardia)
- Sweating
- Anxiety
- Hunger
- Nausea
- Paresthesia of the tongue and face
- Difficulty concentrating, confusion, irritability
- Weakness, dizziness
- Impaired vision, speech or coordination
- Headaches
- Drowsiness
- Loss of consciousness

- Typical symptoms of hyperglycemia[1]
- Fatigue
- Dizziness
- Polyuria
- Polydipsia
- Polyphagia
- Exaggerated hunger
- Unintentional weight loss
- Irritability

Warning signs of ketoacidosis and hyperosmolar hyperglycemic syndrome[1]

- Polyuria
- Polydipsia
- Weakness
- Nausea, vomiting, abdominal pain
- Kussmaul respiration (ketoacidosis)
- Sweet or metallic taste in the mouth (ketoacidosis)
- Acetone breath odour (ketoacidosis)
- Volume depletion
- Blood or urine ketones (ketoacidosis)[2]

[1] This list is not exhaustive.
[2] Ketone testing with blood test strips (which measure beta-hydroxybutyrate) is preferable to testing with urine test strips (which detect acetoacetate).

APPENDIX II - VARIABILITY FACTORS

Blood glucose level[1]

Certain factors can affect the blood glucose level:

- A skipped or delayed meal or snack, malnutrition (↓)
- Diet (e.g., ketogenic, intermittent fasting) (↕)
- Gastroparesis (↓)
- Intense or prolonged physical exercise (↕)
- Taking other medications or alternative treatments (e.g., natural products) (↕)
- Fasting (↕)
- Stress (↕)
- Hormonal changes (↕)
- Decline in cognitive function (↕)
- Antidiabetic dosing error or missed dose (↕)
- Alcohol consumption (↕)
- Hospitalization (↕)
- Intercurrent illness, health problems (e.g., infarction, pulmonary embolism, stroke, acute respiratory failure, pancreatitis, infection, surgery) (↑)
- A decrease in the level of physical activity (e.g., due to an injury) (↑)
- Corticosteroid therapy (↑)
- Occasional overeating or excessive carbohydrate intake (↑)
- Dehydration (↑)

Glycated hemoglobin[1]

The HbA_{1c} level depends on the average lifespan of red blood cells. Since erythrocyte decay is not linear, the mean blood glucose level for the 30 days prior to the test contributes 50% to the HbA_{1c} value.

The HbA_{1c} value should be interpreted with caution, as it may not reflect the person's actual mean blood glucose level, especially in certain ethnic groups. Other factors can also affect HbA_{1c} values and cause a discrepancy with capillary blood glucose values:

↑ HbA_{1c}	↓ HbA_{1c}	↕ HbA_{1c}
Advanced age	Hemolytic anemia	Fetal hemoglobin (pregnancy)
Alcoholism	Rheumatoid arthritis	Hemoglobinopathies
Iron or vitamin B_{12} deficiency	Dapsone	Chronic renal failure
Decreased erythropoiesis	High doses of vitamin C or E	Methemoglobinemia
High aspirin dose	Hemodialysis	
Ethnicity (Africans, Afro-Americans, Asians, Hispanics, Native Americans)	Bleeding	
	Chronic liver failure	
Hyperbilirubinemia	Erythropoietin (EPO) use	
Hypertriglyceridemia	Reticulocytosis	
Therapeutic noncompliance	Splenomegaly	
Splenectomy	Iron or vitamin B_{12} supplements	
Chronic opioid use	Antiretroviral therapy (ribavirin)	
	Recent transfusion	

[1] This list of factors is not exhaustive.

Legend: ↓ : decrease ↑ : increase ↕ : can increase or decrease

APPENDIX III - SUMMARY TABLE OF ANTIDIABETICS

		Hypo-glycemia	Weight	Cardiovascular effect[1, 2]		Renal failure		Details	Mechanism of action	Route of admini-stration	Cost	On the RAMQ's *Liste des médicaments*[1]
				ASCVD	HF	Effect on progression[1, 2]	Adjustment based on eGFR[1]					
Biguanides		No	↔	Neutral	Neutral	Neutral	< 15 ml/min/1.73 m²: ⊗, 15 to 44 ml/min/1.73 m²: ↓ doses.	Gastrointestinal disturbances, ↓B_{12}	↑ cellular insulin sensitivity; ↓ liver glucose production	PO	$	Yes, but not the long-acting form (not covered by the RPAM)
Secretagogues (sulfonylureas and meglitinides)		Yes	↑	Neutral	Neutral	Neutral	Gliclazide, glimepiride: < 15 ml/min/1.73 m²: ⊗; 15 to 29 ml/min/1.73 m²: ⚠ (hypo). Glyburide: < 30 ml/min/1.73 m²: ⊗; 30 to 59 ml/min/1.73 m²: ⚠ (hypo). Repaglinide: safe in RF.	Repaglinide: greater effect on postprandial blood glucose levels	Stimulates pancreatic insulin production	PO	SU $ Repaglinide $$	Yes, but not glimepiride = exception drug
GLP-1 receptor agonists		No	↓	Beneficial: Liraglutide Semaglutide Dulaglutide	Neutral	Neutral: Liraglutide Semaglutide Dulaglutide	Dulaglutide: < 15 ml/min/1.73 m²: ⚠. Exenatide: < 30 ml/min/1.73 m²: ⊗; 30 to 49 ml/min/1.73 m²: ⚠. Liraglutide, lixisenatide, semaglutide: < 15 ml/min/1.73 m²: ⊗; 15 to 49 ml/min/1.73 m²: ⚠.	Gastrointestinal disturbances	Mimics the effect of incretins (intestinal hormones involved in blood glucose control)	SC Semaglutide SC or PO	$$$$	Exception drugs, but not exenatide, lixisenatide or oral semaglutide (not covered by the RPAM)
SGLT2 inhibitors		No	↓	Beneficial: Canagliflozin Empagliflozin Dapagliflozin	Beneficial: Canagliflozin Empagliflozin Dapagliflozin	Beneficial: Canagliflozin Empagliflozin Dapagliflozin	Canagliflozin: < 30 ml/min/1.73 m²: ⊗; 30 to 59 ml/min/1.73 m²: ↓doses. Dapagliflozin: < 25 ml/min/1.73 m²: ⊗; Empagliflozin: < 20 ml/min/1.73 m²: ⊗; < 30 ml/min/1.73 m²: ↓doses.	Diabetic ketoacidosis, hypotension, urinary tract infections, genital yeast infections	Promotes the excretion of glucose in the urine	PO	$$$	Exception drugs
DPP-4 inhibitors		No	↔	Neutral	Potentially harmful: Saxagliptin	Neutral	Alogliptin: < 60 ml/min/1.73 m²: ↓doses. Linagliptin: < 15 ml/min/1.73 m²: ⚠ Sitagliptin, saxagliptin: < 45 ml/min/1.73 m²: ↓doses.	-	↑ the effect of incretins (intestinal hormones involved in blood glucose control)	PO	$$$	Exception drugs
Thiazolidinediones		No	↑	Neutral	Harmful	Neutral	< 60 ml/min/1.73 m²: ⚠.	Edema, bladder cancer (pioglitazone), HF, fractures	↑ action of insulin	PO	$$	Exception drugs
Alpha-glucosidase inhibitors		No	↔	Neutral	Neutral	Neutral	< 25 ml/min/1.73 m²: ⊗	Gastrointestinal problems	Slows the digestion of carbohydrates in the intestine	PO	$$	Yes
Insulin	human	Yes	↑	Neutral	Neutral	Neutral	↓ doses with decreased eGFR	-	-	SC	$-$$$	Yes, except crystalline zinc 500 units/ml (not covered by the RPAM)
	analogues										$$$	Yes but Mix 30 and Mix 25 = exception drugs Rapid aspart and Mix 50 not covered by the RPAM

[1] May not be up to date with the most recent publications.
[2] Was not subjected to a systematic review.
↓ : decrease. ↑ : increase. ↔ : neutral effect. ⊗ : contraindicated or not recommended. ⚠ : exercise caution or titrate with caution.
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; PO: per os; RAMQ: Régie de l'assurance maladie du Québec; RF: renal failure; RPAM: public prescription drug insurance plan; SC: subcutaneous.

APPENDIX IV - ORAL AND INJECTABLE ANTIDIABETICS AVAILABLE IN CANADA

Biguanides	Secretagogues: Sulfonylureas	Secretagogues: Meglitinides	GLP-1 receptor agonists	SGLT-2 inhibitors	DPP-4 inhibitors	Thiazolidinediones	α-glucosidase inhibitors	Combination formulations[1]
Metformin **Extended-release metformin**	Gliclazide Extended-release gliclazide Glimepiride Glyburide	Repaglinide	Dulaglutide Exenatide Extended-release exenatide Liraglutide Lixisenatide Semaglutide Oral semaglutide	Canagliflozin Dapagliflozin Empagliflozin	Alogliptin Linagliptin Saxagliptin Sitagliptin	Pioglitazone[1] Rosiglitazone	Acarbose	Alogliptin/metformin Canagliflozin/metformin Dapagliflozin/metformin Dapagliflozin/saxagliptin Empagliflozin/metformin Empagliflozin/linagliptin Linagliptin/metformin Saxagliptin/metformin Sitagliptin/metformin Liraglutide/degludec insulin Lixisenatide/insulin glargine

[1] This protocol concerns individual formulations. To use this protocol when adjusting combination formulations, see the Frequently Asked Question (FAQ) on this topic.

ANPPENDIX V - MISSED DOSE PROCEDURE[1]

	General principles if a dose is missed: - Do not take a double dose to make up for the missed dose. - Do not take an extra dose or increase the next day's dose to make up for the missed dose.	
Biguanides	**Metformin (regular)**	- Missed dose realized quickly (< 2 hours): take the missed dose. - Missed dose realized later (> 2 hours): do not take the missed dose. Instead, take the next dose at the usual time.
	Metformin (long-acting)	- Take the missed dose as soon as possible before bedtime.
Sulfonylureas **Meglitinides**	**Glyburide** **Gliclazide - regular** **Repaglinide**	- Missed dose realized during or right after a meal: take the missed dose. - Missed dose realized > 30 minutes after a meal: do not take the missed dose. Instead, take the next dose at the usual time.
	Gliclazide (extended release) **Glimepiride**	- Missed dose realized during or right after breakfast: take the missed dose. - Missed dose realized > 1 hour after breakfast: take the missed dose at noon. - Missed dose realized > 1 hour after midday meal: do not take the missed dose. Instead, take the next dose at the usual time.
GLP-1 receptor agonists	**Dulaglutide** **Exenatide (once-weekly)**	- If next dose is in 3 days (72 hours) or more: administer the missed injection. - If next dose is in less than 3 days (72 hours): do not take the missed dose. - Continue with the usual weekly dosing regimen.
	Exenatide - regular **Lixisenatide**	- Do not take the missed dose. - Take the next dose at the usual time.
	Liraglutide	- Missed dose realized within 12 hours: administer the missed injection. - Missed dose realized later (> 12 hours): do not administer the missed injection. Instead, take the next dose at the usual time.
	Semaglutide - injectable	- The missed dose should be administered as soon as possible within 5 days of its occurrence. - If more than 5 days have elapsed since the missed dose, do not administer the missed dose. - Continue with the usual weekly dosing regimen.
	Semaglutide - oral	- Do not take the missed dose. - Take the next dose at the usual time.
SGLT-2 inhibitors	**Canagliflozin** **Dapagliflozin** **Empagliflozin**	- Missed dose realized within 12 hours: take the missed dose. - Missed dose realized later (> 12 hours): do not take the missed dose. Instead, take the next dose at the usual time.
DPP-4 inhibitors	**Alogliptin** **Linagliptin** **Saxagliptin** **Sitagliptin**	
Thiazolidinediones	**Pioglitazone** **Rosiglitazone**	If once-daily dosing: - Missed dose realized within 12 hours: take the missed dose. - Missed dose realized later (> 12 hours): do not take the missed dose. Instead, take the next dose at the usual time. If BID dosing: - Missed dose realized quickly (< 2 hours): take the missed dose. - Missed dose realized later (> 2 hours): do not take the missed dose. Instead, take the next dose at the usual time.
Alpha-glucosidase inhibitors	**Acarbose**	- Do not take the missed dose. - Take the next dose at the usual time.
Insulins	**Degludec**	- Inject the missed daily dose as soon as possible. - Wait at least 8 hours between consecutive injections.
	Aspart **Glulisine** **Lispro** **Rapid aspart**	- The missed dose can be administered immediately after the meal (aspart) or up to 20 minutes after the start of a meal (rapid aspart, glulisine, lispro). - Resume the usual schedule at the next meal.
	Other insulins	- Do not take the missed dose. - Missed-dose management should be done on a case-by-case basis based on clinical judgment.

[1] The information in this table is based on the Canadian product monographs and the experience of the advisory committee's members.