Diabetes

Pharmacological Options and Considerations for Management

Table of Contents

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Diabetes Management Summary

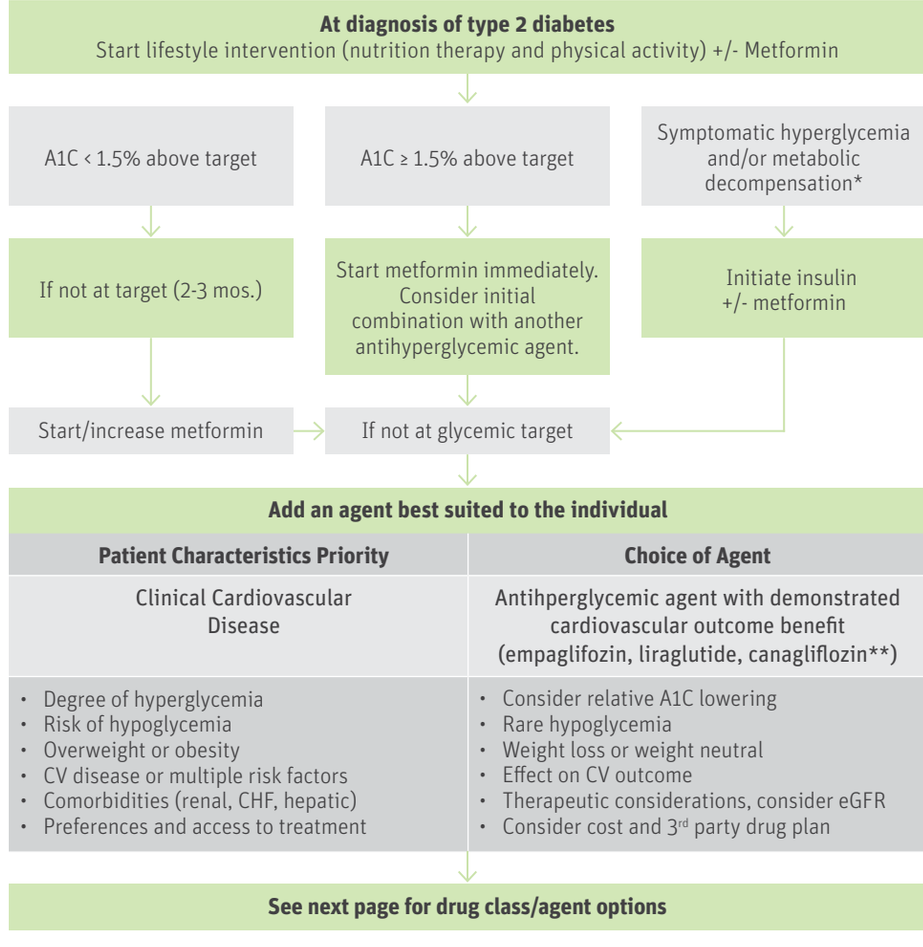
A Resource to Support the Pharmacist's Role in Recommending Diabetes Treatment

There are many issues that must be taken into consideration when helping patients to optimally manage blood glucose levels associated with diabetes. To deliver effective diabetes care, an interprofessional team with the appropriate expertise is required.[1] The care plan should address healthy behaviours, glycemic control, blood pressure control, lipid management, and vascular protection. This approach has been shown to effectively and significantly lower the risk of development and progression of serious complications for individuals with diabetes.[1]

Pharmacists are the medication experts on the interprofessional team. This Diabetes Counselling Guide has been designed to aid pharmacists in helping their patients manage blood glucose effectively. It includes evidence-based information regarding blood glucose targets, monitoring schedules, lifestyle modification, and pharmacotherapy considerations. Antihyperglycemic options are listed in detail, with important treatment considerations outlined in a systematic fashion for each available medication. When antihyperglycemic pharmacotherapy is indicated, the guide supports pharmacists in advising patients about the reasons for recommending treatment and the benefits and risks associated with various options. In this manner, pharmacists are able to help patients make informed decisions about treatment.

At times, pharmacists may need to address concerns that arise when a patient receives a generic version of the previous medication. They can do this by using simple language to explain processes in place to ensure quality of the generic version. The quality standards for brand name drugs and generic drugs are the same; the ingredients, manufacturing processes, and facilities for all drugs must meet the federal guidelines for Good Manufacturing Practices.[2] In order to be deemed bioequivalent, the generic drug manufacturer must conduct comparative bioavailability studies. In these studies, the level of a medicinal ingredient in the blood of healthy human volunteers is measured. During the studies, each volunteer gets the brand name drug and the new generic drug. The generic drug must show that it delivers the same amount of medicinal ingredient at the same rate as the brand name drug.[2] Non-medicinal ingredients, such as fillers and ingredients that colour the drug, may be different from those of the brand name product.[2] The generic manufacturer must provide studies showing that the different non-medicinal ingredients have not changed the quality, safety, or effectiveness of the generic drug.[2]

Management of Type 2 Diabetes: Diabetes Canada Guidelines Algorithm[3]



1. The presence of clinical cardiovascular disease and the effect of antihyperglycemic agents on cardiovascular outcomes should be considered the top priority in choosing add-on treatment regimens for patients with type 2 diabetes.
2. If the major clinical consideration associated with treatment is avoidance of hypoglycemia and/or weight gain with adequate glycemic efficacy, then a DPP-4 inhibitor, GLP-1 receptor agonist or SGLT2 inhibitor should be primary considerations for add-on therapy.
3. See "Pharmacological Options" section for therapeutic considerations associated with each antihyperglycemic agent as related to individualized patient needs.

*May include dehydration, DKA, HHS
**Avoid in people with lower extremity amputation

From previous page

Add an agent best suited to the individual[3]
(Drug classes listed in alphabetical order)

Class	Antihyperglycemic Drugs in Class
Alpha-glucosidase inhibitor	Acarbose
Incretin agents:	
DPP-4 inhibitors	Linagliptin, sitagliptin, saxagliptin, alogliptin
GLP-1 receptor agonists	Exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide
Insulin:	
Basal	NPH Insulin, detemir, glargine (100 U/mL, 300 U/mL), degludec (U-100, U-200)
Bolus Rapid-acting	Aspart, aspart (faster acting), glulisine, lispro (U-100, U-200), human biosynthetic (U-500)
Bolus Short-acting	Humulin® R, Novolin® ge Toronto
Premixed regular insulin-NPH	Humulin® 30/70, Novolin® ge 30/70, 40/60, 50/50
Premixed insulin analogues	Biphasic insulin aspart (NovoMix® 30), Insulin lispro/lispro protamine (Humalog® Mix25® and Mix50®)
Insulin secretagogue:	
Meglitinide	Repaglinide
Sulfonylureas	Gliclazide, glimepiride, glyburide
Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors*	Canagliflozin, dapagliflozin, empagliflozin
Thiazolidinediones	Pioglitazone, rosiglitazone
Weight loss agent	Orlistat

If not at glycemic target

Add another agent from a different class or add/intensify insulin

Make timely adjustments to attain target A1C within 3 to 6 months

Acronym key:
A1C = Hemoglobin A1C BG = Blood glucose DKA = Diabetic ketoacidosis
DPP-4 = Dipeptidyl peptidase-4 GLP-1 = Glucagon-like peptide-1
CHF = Congestive Heart Failure eFFR = estimated Glomerular Filtration Rate
HHS = Hyperosmolar hyperglycemic state

Discuss Patient's Glycemic Targets

In epidemiological studies, hemoglobin A1C (A1C) values above 7.0% have been associated with significantly increased risk of microvascular and macrovascular complications.[4] Therefore, control of blood glucose is fundamental to the management of diabetes.[4] Fasting plasma glucose and postprandial plasma glucose are both directly correlated to the risk of diabetes complications.[4]

The following recommendations for glycemic targets have been based on the best available evidence from randomized controlled trials:[4]

- Most patients with type 1 and type 2 diabetes should strive for A1C values of 7.0% or less.
- An A1C target of 6.5% or less may be sought in some patients with type 2 diabetes to further lower the risk of nephropathy and retinopathy, provided the patient is at low risk of hypoglycemia.

In order to achieve an A1C of 7% or less, people with diabetes should aim for a fasting plasma glucose or preprandial plasma glucose target of 4.0-7.0 mmol/L and a 2-hour postprandial (PPG) glucose target of 5.0-10.0 mmol/L.[4] If an A1C target of 7% or less cannot be achieved with a PPG target of 5.0-10.0 mmol/L, further lowering to 5.0-8.0 mmol/L should be achieved.[4]

- It is recommended that patients in the following circumstances consider an A1C target of 7.1% - 8.5%:
  - Limited life expectancy
  - Frail elderly and/or with dementia
  - History of recurrent severe hypoglycemia
  - Hypoglycemia unawareness

It is recommended functionally dependent patients target an A1C of 7.1-8.0%

Measurement of A1C is not recommended for patients at end of life. Symptomatic hyperglycemia and any hypoglycemia should be avoided.

Assess Patient's Glycemic Control

The best information for assessment of glycemic control is obtained through measurement of glycated hemoglobin (A1C) and self-monitoring of blood glucose (SMBG).[5]

The 2018 Diabetes Canada Guidelines recommend that A1C be measured every three months when glycemic targets are not being met and when diabetes therapy is being adjusted.[5] Testing of A1C more often may be appropriate. For example, a patient may need more frequent testing when significant changes are made to therapy or during pregnancy. If glycemic targets are being met and diabetes therapy is not being adjusted, testing at six-month intervals may be considered.[5]

SMBG serves a number of purposes, depending on patient circumstances:[5]

- It is the only way to confirm and appropriately treat hypoglycemia.
- It provides feedback on the impact on glycemia.
- It increases patient empowerment and adherence to treatment of lifestyle and pharmacological treatments.
- It can provide information to patients and healthcare professionals to facilitate longer-term treatment decisions (e.g., insulin dosing).
- It is essential in situations where A1C does not accurately reflect glycemia (i.e., factors that affect erythropoiesis, altered glycation, erythrocyte destruction or assays).

Type 1 Diabetes — Monitor Regularly

For people with type 1 diabetes, conducting at least three blood glucose self-tests daily has been associated with a statistically and clinically significant absolute reduction in A1C of 1%.[5] In order to reduce hypoglycemia risk—including unrecognized nocturnal hypoglycemia—more frequent preprandial, two-hour postprandial blood glucose testing, and occasional nocturnal blood glucose testing are often required.[5]

People with type 1 diabetes should perform ketone testing during periods of acute illness accompanied by elevated blood glucose, when preprandial blood glucose levels remain > 14.0 mmol/L, or in the presence of symptoms of diabetic ketoacidosis (e.g., nausea, vomiting or abdominal pain).[5] Blood ketone testing methods may be preferred over urine ketone testing, since earlier detection of ketosis and response to treatment may result.[5]

Type 2 Diabetes – Monitor According to Patient Circumstances

Patients with type 2 diabetes not using insulin

The benefits of SMBG with respect to improving glycemic control for people with type 2 diabetes treated with lifestyle management, with or without oral antihyperglycemic agents, is not entirely clear.[5] Evidence suggests that SMBG is most effective in persons with type 2 diabetes within the first six months after diagnosis.[5] The 2018 Diabetes Canada Guidelines recommend that SMBG in this patient population should be individualized depending on type of antihyperglycemic agents, level of glycemic control, and risk of hypoglycemia.[5]

- If a patient is having issues with glycemic control, SMBG should be instituted and should include periodic pre- and postprandial measurements. Patients should be trained on methods to modify lifestyle and medications in response to SMBG values.[5]
- Infrequent SMBG is appropriate if the patient is achieving glycemic targets or receiving medications not associated with hypoglycemia.[5]

Patients with type 2 diabetes who are using insulin

For individuals with type 2 diabetes who use two or more injections of insulin a day, the monitoring recommendations outlined on the previous page for patients with type 1 diabetes apply.[5]

For individuals with type 2 diabetes who use one basal dose of insulin daily in addition to oral antihyperglycemic agents, it is recommended that monitoring be conducted at least once a day at various times of the day.[5]

Note: SMBG guidelines and glycemic targets for pregnancy can be found in the 2018 Diabetes Canada Clinical Practice Guidelines at http://guidelines.diabetes.ca/browse/chapter36 SMBG guidelines and glycemic targets for children can be found at http://guidelines.diabetes.ca/browse/chapter34 (type 1 diabetes) and http://guidelines.diabetes.ca/browse/chapter35 (type 2 diabetes).

Recommending Patterns of SMBG

An excellent guide for determining SMBG pattern recommendation according to patient circumstances can be found on the Diabetes Canada website at *http://guidelines.diabetes.ca/CDACPG_resources/SMBGpatterns.pdf*.

In addition, a self-monitoring of blood glucose recommendation tool for healthcare providers can be found at *http://guidelines.diabetes.ca/self-management/smbg-tool*.

Below is an example of monitoring pattern recommendations for individuals not using insulin, with a diagnosis of type 2 diabetes in the past six months or not meeting targets. A basic monitoring pattern and a pattern developed to learn the effect of various meals are illustrated.[6]

The charts as shown on the website cited are excellent resources for patient education and adherence.

In general, the patient should check at least once each day, at different times of day, to learn the effects of various meals, exercise, and medications on blood glucose.

SMBG Basic Pattern

	Breakfast		Lunch		Supper		Bedtime	Night
	Before	After	Before	After	Before	After		
Sunday								
Monday								
Tuesday								
Wednesday								
Thursday								
Friday								
Saturday								

SMBG Pattern to Learn the Effects of Various Meals

	Breakfast		Lunch		Supper		Bedtime	Night
	Before	After	Before	After	Before	After		
Sunday								
Monday								
Tuesday								
Wednesday								
Thursday								
Friday								
Saturday								

Discuss Lifestyle Modifications that May Improve Health and Glycemic Control

As outlined in the 2018 Diabetes Canada Guidelines, intensive lifestyle interventions in people with type 2 diabetes can produce improvements in weight management, fitness, glycemic control, and cardiovascular risk factors.

Physical activity benefits include increased cardiorespiratory fitness, increased vigour, improved glycemic control, decreased insulin resistance, improved lipid profile, blood pressure reduction, and maintenance of weight loss.[7]

Both aerobic and resistance exercise are beneficial for patients with diabetes.[7] It is recommended that people with diabetes accumulate at least 150 minutes of moderate-vigorous aerobic activity each week, spread over at least 3 days a week as well as resistance exercise 2 or 3 times a week.

- Aerobic exercise includes activities that involve continuous, rhythmic movements of large muscle groups—such as walking, bicycling or jogging.
- Resistance exercise involves brief repetitive exercises with weights, weight machines, resistance bands, or one's own body weight (e.g., pushups) to increase muscle strength and/or endurance.

Nutrition therapy can reduce A1C by 1% to 2%. When used with other components of diabetes care, it can further improve clinical and metabolic outcomes, resulting in reduced hospitalization rates.[8] In general, individuals with diabetes should be encouraged to follow *Eating Well with Canada's Food Guide* to meet their nutritional needs.[8] Specific nutrition therapy guidance for people with diabetes, including the role of glycemic index in glycemic control, can be found in the Diabetes Canada Clinical Practice Guidelines at http://guidelines.diabetes.ca/cpg/chapter11.

Weight loss of 5% to 10% of initial body weight can substantially improve glycemic control and cardiovascular disease risk factors in people with type 2 diabetes.[9] The drug effects on body weight should be considered when choosing antihyperglycemic therapy.

Insulin, thiazolidinediones, and insulin secretagogues such as sulfonylureas are more likely to cause weight gain, while DPP-4 inhibitors, incretins, metformin and SGLT2 inhibitors are more likely to be weight neutral, or in some cases contribute to weight loss. Orlistat is a drug designed to promote weight loss but does not have a direct antihyperglycemic effect.

Review of Available Treatment Options

The choice of medication for management of diabetes is aided by the recommendations of the 2018 Diabetes Canada Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada and should take into account the prescriber's clinical judgment and the preferences of the patient.

Pharmacotherapy

Pharmacological options for management of diabetes include:*

- Alpha-glucosidase inhibitor: acarbose
- DPP-4 inhibitors: sitagliptin, saxagliptin, linagliptin, alogliptin
- GLP-1 receptor agonists (Incretins): exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide
- Insulins
  - Bolus (prandial) insulins
    - Ultra fast-acting analogue: aspart (faster acting)
    - Rapid-acting analogues: aspart, glulisine, lispro
    - Short-acting: regular insulin, human biosynthetic insulin
  - Basal insulins
    - Intermediate-acting: NPH
    - Long-acting basal analogues: detemir, glargine, degludec
  - Premixed insulins
    - Regular insulin-NPH
    - Insulin analogues
- Meglitinide: repaglinide
- Metformin
- SGLT2 inhibitors: canagliflozin, dapagliflozin, empagliflozin
- Sulfonylureas: gliclazide, glimepiride, glyburide
- Thiazolidinediones: pioglitazone, rosiglitazone

Acronym key:
DPP-4 = Dipeptidyl peptidase-4 GLP-1 = Glucagon-like peptide-1
SGLT2 = Sodium-glucose co-transporter 2

***Please note: Only single agent antidiabetes medications have been presented. Antidiabetes agents are often used together and may even be combined in a single product. Please refer to individual product monographs and specific product monographs for combined drug therapies for more information.**

Pharmacological Options

Pharmacological Options:
Alpha-Glucosidase Inhibitor
(Acarbose)

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for acarbose.

Contraindications[10]

- Patients who are hypersensitive to acarbose or to any ingredient in the formulation or component of the container
- Inflammation or ulceration of the bowel (e.g., ulcerative colitis or Crohn's disease) or partial intestinal obstruction or predisposed to intestinal obstruction
- Diabetic ketoacidosis
- Bowel obstruction
- Chronic intestinal diseases that affect digestion or absorption of food, or patients who suffer from states that may deteriorate as a result of increased gas formation in the intestine such as large hernia

Inform patients about possible warnings and precautions associated with acarbose therapy.

- In combination with a sulfonylurea or insulin, acarbose may cause hypoglycemia.[10]

Before taking acarbose, patients should talk with their doctor or pharmacist if they:[10]

- Have or have had kidney or liver disease
- Are pregnant or planning to become pregnant
- Are breastfeeding

Acarbose is not recommended for children under 18 years of age.

Inform patients about possible interactions with acarbose.

Patients should talk with their doctor or pharmacist before taking any other medicine in addition to acarbose—including over-the-counter products—as the following list of interactions are not comprehensive.[10]

- Drugs that interact with acarbose include digestive enzyme preparations, cholestyramine, diuretics (water pills), corticosteroids (such as prednisone), digoxin, thyroid medications, estrogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid.
- Patients should avoid drinking alcohol while taking acarbose.

Inform patients about side effects associated with acarbose.[10]

- The most common side effects associated with acarbose are gastrointestinal in nature, such as flatulence (gas) and abdominal discomfort.
- Patients may pass softer stools or even experience diarrhea, particularly after a meal containing foods with sucrose. Normally, these symptoms will diminish with continued treatment. Patients should not take antacid preparations for treating these symptoms, as they are unlikely to have any beneficial effects. If symptoms persist, or if any other undesirable effects occur, patients should consult their doctor.
- Acarbose, when given alone, should not cause hypoglycemia. However, since sulfonylureas or insulin may cause hypoglycemia, the combination of a sulfonylurea or insulin and acarbose may also cause hypoglycemia. If a patient does experience hypoglycemia while taking acarbose—either alone or with a sulfonylurea, metformin, or insulin—the symptoms should be treated with glucose tablets.

The following serious side effects have been reported with the use of acarbose:[10]

- *Uncommon (talk with doctor or pharmacist only if severe):* Nausea, vomiting, abdominal pain
- *Rare (patient should talk with doctor or pharmacist only if severe):* Edema
- *Rare (patient should stop taking drug and call doctor or pharmacist):* Jaundice
- *Very Rare (patient should talk with doctor or pharmacist in all cases):* Allergic reactions: rash, skin inflammation

This is not a complete list of side effects. For any unexpected effects while taking acarbose, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
(Linagliptin, Saxagliptin, Sitagliptin, Alogliptin)

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for DPP-4 inhibitors.

Contraindications

- Linagliptin, saxagliptin, sitagliptin and alogliptin should not be used by patients who have type 1 diabetes or diabetic ketoacidosis.[11-14]
- Patients who are hypersensitive to the drug or to any ingredient in the formulation.

Inform patients about possible warnings and precautions associated with DPP-4 inhibitor therapy.

Before taking any DPP-4 inhibitor, patients should talk with their doctor or pharmacist if they:[11-14]

- Take insulin
- Have had an allergic reaction to other DPP-4 inhibitors
- Have had pancreatitis or any risk factors for pancreatitis such as gallstones, a history of alcoholism, or high triglyceride levels
- Have had kidney problems
- Have had liver problems
- Have heart failure or any other heart condition
- Are pregnant, planning to become pregnant, breastfeeding, or planning to breastfeed
- Are taking a sulfonylurea

In addition, before taking saxagliptin, patients should talk with their doctor or pharmacist if they:[12]

- Have been told that they have a reduced immune system (e.g., organ transplantation or diagnosis of human immunodeficiency syndrome)

In addition, before taking linagliptin, patients should talk with their doctor or pharmacist if they:[11]

- Have any skin problems

In addition, before taking alogliptin, patients should talk with their doctor or pharmacist if they:[14]

- Have type 1 diabetes
- Have diabetic ketoacidosis
- Have, or have had, liver problems
- Suffer from heart failure
- Have, or have had, kidney disease
- Have any allergies,
- Have, or have had, inflammation of the pancreas
- Have had allergic reactions to any other medications that are taken to control blood glucose
- Are taking the antihyperglycemic medications pioglitazone and metformin
- Have had allergic reactions with symptoms to any other antihyperglycemics that include general itching and feeling of heat especially affecting the scalp, mouth, throat, palms of hands and soles of feet, as well as blistering (Stevens-Johnson syndrome)

Inform patients about possible interactions with DPP-4 inhibitor therapy.

Patients should tell their doctor or pharmacist about all the drugs they take, including prescription and non-prescription drugs, including herbal supplements.[11-14]

The metabolism of DPP-4 inhibitors is primarily mediated by CYP 3A4/5; however, drug-drug interaction with other inhibitors or inducers (such as warfarin, digoxin, etc.) is not clinically significant.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
(Linagliptin, Saxagliptin, Sitagliptin, Alogliptin)

Inform patients about side effects associated with DPP-4 inhibitors.

Linagliptin

Very common side effects associated with linagliptin include:[11]

- Hypoglycemia when taken with a sulfonylurea. Patients should stop taking linagliptin and see their doctor immediately if experiencing symptoms of low blood sugar such as trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change, vagueness, or confusion.

Uncommon side effects associated with linagliptin include:[11]

- Cough
- Nasopharyngitis
- High triglyceride levels
- Hives or nettle rash (urticaria)

Rare side effects associated with linagliptin include:[11]

- Rash

The following serious side effects have been reported with the use of linagliptin:[11]

- *Uncommon (patients should stop taking the drug and call their doctor or pharmacist immediately):* Severe allergic reaction-swelling of the face, lips, mouth, tongue, or throat that may cause difficulty in swallowing or breathing (angioedema)
- *Rare (patients should stop taking the drug and call their doctor or pharmacist immediately):* Pancreatitis: symptoms include prolonged severe abdominal pain which may be accompanied by vomiting

This is not a complete list of side effects. For any unexpected effects while taking linagliptin, patients should be informed to contact their doctor or pharmacist.

Saxagliptin

Common side effects of saxagliptin include upper respiratory tract infection, urinary tract infection, and headache.[12]

Hypoglycemia may occur more frequently in people who already take a sulfonylurea or insulin. If patients have symptoms of hypoglycemia, they should check their blood glucose and treat if low, and then call their healthcare provider.[12]

Heart failure may occur more frequently in people taking saxaglipin.[3]

The following serious side effects have been reported with use of saxagliptin:[12]

- *Uncommon (patients should talk with their doctor or pharmacist only if severe):* Rash
- *Uncommon (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Pancreatitis: symptoms include prolonged severe abdominal pain which may be accompanied by vomiting
- *Very Rare (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Allergic reaction: hives; swelling of face, lips, or throat

This is not a complete list of side effects. For any unexpected effects while taking saxagliptin, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
(Linagliptin, Saxagliptin, Sitagliptin, Alogliptin)

Sitagliptin

The most common side effects of sitagliptin include stuffy or runny nose and sore throat.[13]

Very common side effects associated with sitagliptin include:[13]

- Hypoglycemia when taken with a sulfonylurea. Patients should speak with their doctor or pharmacist in all cases if experiencing symptoms of low blood sugar such as trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change, vagueness, or confusion.

Additional side effects reported with use of sitagliptin include:[13]

- Vomiting
- Constipation
- Headache
- Joint pain

The following serious side effects have been reported with the use of sitagliptin:[13]

- *Rare (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Pancreatitis: symptoms include prolonged severe abdominal pain which may be accompanied by vomiting.
- *Rare (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Allergic reactions including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.
- *Rare (patients should call their doctor or pharmacist in all cases):* Acute kidney failure: symptoms may include nausea, loss of appetite and weakness, pass little or no urine, breathlessness. If a patient experiences this reaction, he/she should call a doctor or pharmacist immediately.

This is not a complete list of side effects. For any unexpected effects while taking sitagliptin, patients should be informed to contact their doctor or pharmacist.

Alogliptin

Common side effects of alogliptin include cold or flu-like symptoms such as sore throat, stuffy or blocked nose, feeling tired, fever, chills, body ache, dry cough; rash; itchy skin, headache, stomach pain, nausea, toothache, vomiting, constipation, indigestion, heartburn; malaise; back pain, muscle and bone pain; muscle spasms; fatigue; insomnia; anemia; neutropenia; peripheral edema; upper respiratory tract infection; nasopharyngitis; hypercholesterolemia or dyslipidemia; arthralgia; diabetic neuropathy; hypertension.[14]

Uncommon side effects reported with use of alogliptin include allergic reaction and pancreatitis.[14]

Side effects with unknown frequency that may occur include severe allergic reaction (Stevens-Johnson syndrome) and liver problems.[14]

The following serious side effects have been reported with use of alogliptin:[14]

- *Common (patients should stop taking the drug and call their doctor or pharmacist in all cases):* [when used with metformin and pioglitazone, or with a sufonylurea, or when used with insulin with or without metformin] Hypoglycemia
- *Uncommon (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Allergic reaction (rash, hives, swallowing or breathing problems, swelling of lips, face, throat, tongue and feeling faint)
- *Uncommon (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Pancreatitis: symptoms include prolonged severe abdominal pain which may be accompanied by vomiting
- *Unknown (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Stevens-Johnson syndrome (symptoms may include rash, skin reddening, pain, swelling of lips, eyes or mouth, skin peeling and flu-like symptoms)
- *Unknown (patients should stop taking the drug and call their doctor or pharmacist in all cases):* Liver problems such as nausea or vomiting, stomach pain, unusual or unexplained tiredness, loss of appetite, dark urine or yellowing of skin or whites of eyes

This is not a complete list of side effects. For any unexpected effects while taking alogliptin, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists (Incretins)[15-20]

(Exenatide, Lixisenatide, Liraglutide, Semaglutide, Dulaglutide)

Ensure that therapy is right for your patient.

Please note: Although albiglutide has been approved for use in Canada at time of publication, the product has not been marketed and the product monograph was not generally available at time of publication. Therefore, specific information about albiglutide is not included in following section.

Please see Table 1 for indications and associated doses for GLP-1 receptor agonists.

Contraindications

- Exenatide should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min), including patients receiving dialysis.[15]
- GLP-1 receptor agonists are contraindicated in patients with diabetic ketoacidosis, diabetic coma/precoma, or type 1 diabetes mellitus.[15]
- Exenatide, dulaglutide, liraglutide and semaglutide are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).[16]
- GLP-1 receptor agonists should not be used by pregnant or breastfeeding women.
- GLP-1 receptor agonists are contraindicated in patients with known hypersensitivity to this product or any of its components.

Serious Warnings and Precautions:

- Caution is advised when prescribing lixisenatide in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.
- Exenatide, lixisenatide, and semaglutide have been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis.

Inform patients about possible warnings and precautions associated with GLP-1 receptor agonist therapy.

Before taking any GLP-1 receptor agonists, patients should talk with their doctor or pharmacist if they:[15,16]

- Have severe problems with gastroparesis or food digestion
- Have severe vomiting and/or diarrhea and/or dehydration
- Have a history of pancreatitis, gallstones, alcoholism, or high blood triglyceride levels
- Are receiving treatment with a sulfonylurea (e.g., glyburide, gliclazide, glimepiride) or insulin, since these types of drugs can increase the risk of hypoglycemia if used in combination with GLP-1 degradation inhibitors
- Have had kidney disorder or kidney transplant
- Are pregnant or planning to become pregnant
- Are breastfeeding or plan to breastfeed
- Have currently or have a history of heart failure or other heart disease, such as angina or heart rhythm disturbances, or a history of myocardial infarction
- Have a personal history of fainting spells
- Have high heart rate or a heart block
- Have electrolyte disturbances (e.g., low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)
- Have ever had medullary thyroid cancer or have a family member who has had medullary thyroid cancer
- Have multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Have type 1 diabetes
- Have ever had diabetic ketoacidosis
- Have been diagnosed with pituitary or adrenal failure
- Have any eating disorders, are on a special diet, or often skip meals
- Exercise regularly or intensely
- Drink alcohol excessively

In addition, before taking liraglutide, patients should talk with their doctor or pharmacist if they have liver problems.[16] When initiating treatment with liraglutide patients may in some cases experience loss of fluids/dehydration.

Liraglutide and dulaglutide may increase heart rate and could cause changes known as PR prolongation, which are detected by electrocardiogram (ECG) tracings.

Semaglutide use increased risk for diabetic retinopathy complications, especially in patients with a history of diabetic retinopathy at baseline.

Pharmacological Options: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists (Incretins)[15-20]

(Exenatide, Lixisenatide, Liraglutide, Semaglutide, Dulaglutide)

Inform patients about possible interactions with GLP-1 receptor agonist therapy.

Patients should talk with their doctor or pharmacist before taking any other medicine in addition to GLP-1 receptor agonists, including over-the-counter products as the following lists of interactions are not comprehensive.

Exenatide and Lixisenatide

Exenatide and lixisenatide slow stomach emptying and can affect medicines that need to pass through the stomach quickly. Patients should ask their doctor or pharmacist if the time at which they take any of their oral medicines (for example, birth control pills, antibiotics) should be changed. In particular, patients should tell their doctor or pharmacist if they are taking:

- An oral contraceptive, this medication should be taken at least one hour before taking exenatide
- An antibiotic, this medication should be taken at least one hour before taking exenatide
- Warfarin, digoxin, lisinopril, acetaminophen, lovastatin

All GLP-1 Receptor Agonists

Before taking a GLP-1 receptor agonist, patients should tell their doctor or pharmacist if they are taking:

- A sulfonylurea or insulin
- Any of the following drugs that may increase the risk of arrhythmias: anti-arrhythmic drugs, antivirals to treat HIV infection, diuretics, antihypertensives, beta-blockers, decongestants, stimulants, sympathomimetics (not a complete list)

Lixisenatide

The following is a very common side effect (affects more than one in 10 people):[19]

- Nausea (which goes away over time)

The following are less common side effects (affect more than one in 100 and less than one in 10 people):

- Vomiting, diarrhea, dyspepsia, constipation, bloating, upper abdominal pain, asthenia, fatigue, decreased appetite, back pain, headache, dizziness, tremor, injection site reactions

The following serious side effects have been reported with the use of lixisenatide:[19]

- *Common (patients should contact doctor or pharmacist only if severe)*: Hypoglycemia, change in mood, change in vision, confusion, dizziness, fast heartbeat, feeling faint, headache, hunger, shaking, sweating, weakness
- *Uncommon (patients should stop taking drug and get immediate medical help)*: Pancreatitis (prolonged severe abdominal pain which may be accompanied by vomiting; pain may spread out towards the back); dehydration from prolonged nausea, vomiting or diarrhea, or from not taking enough liquids by mouth (lightheadedness and fainting particularly upon standing); kidney problems including kidney failure (any change in the amount, frequency, or colour of urine); severe allergic reactions including anaphylaxis and angioedema (difficulty breathing or swallowing, itching, hives, fainting, sudden swelling of the face, lips, tongue or throat, rash, very fast heartbeat)

This is not a complete list of side effects. For any unexpected effects while taking lixisenatide, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists (Incretins)[15-20]

(Exenatide, Lixisenatide, Liraglutide, Semaglutide, Dulaglutide)

Inform patients about side effects associated with GLP-1 receptor agonist therapy.

Exenatide

The most common side effects with exenatide include nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, acid stomach, and heartburn.[15]

Hypoglycemia is a common serious side effect when exenatide is used with a sulfonylurea or insulin.[15]

Exenatide may cause new or worsening problems with kidney function, including kidney failure.

Injection site reactions (e.g., rash, itching, bruising) have been reported.

The following rare but serious side effects have been reported with the use of exenatide:

- *Patient should stop taking medication and talk with a doctor or pharmacist if the following occur:*[15]
  - Prolonged severe abdominal pain, which may be accompanied by vomiting. These may be symptoms of pancreatitis.
  - Prolonged nausea, vomiting, and/or diarrhea, or cannot take liquids by mouth. These may increase the risk of kidney problems.
  - Sudden swelling of the face, lips, tongue, or throat; problems breathing or swallowing; severe rash or itching; fainting; very rapid heartbeat. These may be symptoms of angioedema or severe allergic reactions, including anaphylaxis.

This is not a complete list of side effects. For any unexpected effects while taking exenatide, patients should be informed to contact their doctor or pharmacist.

Liraglutide

The following are very common side effects (affect more than one in 10 people):

- Nausea (which usually goes away over time), diarrhea[16]

The following are common side effects (affect fewer than one in 10 people):[16]

- Hypoglycemia, headache, vomiting, burping, indigestion, gastritis, gastroesophageal reflux disease (GERD), constipation, flatulence, upper airways infection, urticaria

The following serious side effects have been reported with the use of liraglutide:[16]

- *Uncommon (patient should stop taking medication and seek immediate medical attention):* Chest pain or symptoms of a possible heart rhythm disturbance/dizziness, palpitations, fainting, or seizures
- *Rare (patient should talk with doctor or pharmacist):* Pancreatitis/persistent, severe abdominal pain with or without vomiting
- *Rare (patient should talk with doctor or pharmacist):* Severe hypoglycemia/disorientation, loss of consciousness, and seizures
- *Rare (patient should stop taking medication and seek immediate medical attention):* Angioedema (symptoms of breathing problems, swelling of throat and face, and tachyarrhythmia)
- *Very Rare (patient should talk with doctor or pharmacist):* Thyroid tumour/lump in the neck, difficulty in swallowing, difficulty in breathing, or persistent hoarsenesss

This is not a complete list of side effects. For any unexpected effects while taking liraglutide, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists (Incretins)[15-20]

(Exenatide, Lixisenatide, Liraglutide, Semaglutide, Dulaglutide)

Semaglutide

The following are very common side effects (affect more than one in 10 people):[20]

- Nausea (which goes away over time), diarrhea

The following are less common side effects (affect more than one in 100 and less than one in 10 people):

- Abdominal pain, vomiting, constipation, dyspepsia, bloating, gastroesophageal reflux disease, fatigue, decreased appetite, dizziness

The following serious side effects have been reported with the use of semaglutide:[20]

- *Common (patients should always contact doctor or pharmacist):* Diabetic retinopathy complications (complications of diabetic eye disease/diabetic eye problems)
- *Uncommon (patients should talk with their health professional in all cases):* Severe hypoglycemia (change in mood, change in vision, confusion, dizziness, fast heartbeat, feeling faint, headache, hunger, shaking, sweating, weakness)
- *Uncommon (patients should stop taking drug and get immediate medical attention):* Pancreatitis (prolonged severe abdominal pain which may be accompanied by vomiting; pain may spread out towards the back)
- *Rare (patients should stop taking drug and get immediate medical attention):* Anaphylactic reaction symptoms (breathing problems, swelling of face and throat, and fast heartbeat)

This is not a complete list of side effects. For any unexpected effects while taking semaglutide, patients should be informed to contact their doctor or pharmacist.

Dulaglutide

The following are very common side effects (affect one or more people out of 10):[17]

- Nausea, diarrhea, vomiting, abdominal pain, hypoglycemia (when used in combination with other antihyperglycemics [especially metformin, insulin, or secretagogues])

The following are common side effects (affect more than one in 100 and less than one in 10 people):

- Decreased appetite, dyspepsia, constipation, flatulence, abdominal distension, heartburn, belching, fatigue, sinus tachycardia, first degree atrioventricular block, hypoglycemia when used as monotherapy and in combination with metformin and pioglitazone

Injection site reactions are uncommon, occurring in less than one in 100 people.

The following serious side effects have been reported with use of dulaglutide:

- *Uncommon (patients should speak with their doctor or pharmacist in all cases):* Severe hypoglycemia symptoms (disorientation, loss of consciousness, or seizures), thyroid tumour symptoms (lump in the neck, difficulty in swallowing, difficulty in breathing or persistent hoarseness)
- *Uncommon (patients should stop taking drug and seek immediate medical attention):* Atrial fibrillation/flutter, irregular heart rate, palpitations, fatigue or shortness of breath
- *Rare (patients should seek immediate medical attention):* Anaphylactic reaction symptoms (breathing problems, swelling of throat and face, and fast heartbeat), pancreatitis symptoms (prolonged severe abdominal pain with or without vomiting)

This is not a complete list of side effects. For any unexpected effects while taking dulaglutide, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Insulins

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for bolus and basal insulins.

See also Table 2 for available insulins as well as dosage forms.

Contraindications

All insulins are contraindicated during episodes of hypoglycemia.

Inform patients about possible warnings and precautions associated with insulin.

Serious Warnings and Precautions[21-30]

- Hypoglycemia is the most common adverse effect of insulin products. As with all insulin products, the timing of hypoglycemia may differ. Glucose monitoring should be performed for all patients with diabetes mellitus treated with insulins.
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or even death.
- Any transfer of insulin products should be made cautiously and only under medical supervision.
- Insulin aspart should be given immediately before a meal, because of the fast onset of action (start of the meal should be not more than five to 10 minutes after injection).
- Insulin aspart (faster acting) should be given up to two minutes before the start of a meal and if necessary may be given up to 20 minutes after starting the meal.
- When used as a mealtime insulin, the dose of insulin glulisine should be given within 15 minutes before or within 20 minutes after starting a meal.
- Insulin lispro should be given within 15 minutes before a meal. When necessary, insulin lispro may be given shortly after a meal instead (within 20 minutes of the start of the meal).
- When used in a subcutaneous insulin infusion pump, insulin lispro should not be diluted or mixed with any other insulin. Patients should carefully read and follow the insulin infusion pump manufacturer's instructions before use.
- Regular insulin injection should be followed by a meal (within 30 minutes).
- Short-acting insulins should be combined with a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.
- Insulin products should not be mixed with any other insulin unless clearly indicated, and then done only under medical supervision.
- Rapid-acting and short-acting insulin products, as well as insulin detemir and insulin glargine, should not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the vial or cartridge.
- NPH insulin shall not be used if the resuspended liquid does not appear uniformly white and cloudy or if it has formed a deposit of solid particles on the wall of the vial or cartridge after resuspending.
- Due to the risk of precipitation in some pump catheters, regular insulin is not recommended for use in insulin pumps.
- Long-acting insulin products and/or suspensions such as intermediate-acting (NPH) and premixed insulins must not be used in an insulin infusion pump.

Before using insulin, patients should talk to their doctor, diabetes nurse educator or pharmacist: [21-30]

- If the patient has trouble with his/her kidneys or liver or with adrenal, pituitary, or thyroid glands, the doctor may decide to alter their insulin dose.
- If the patient drinks alcohol (including wine and beer), the need for insulin may change as blood sugar level may either rise or fall.
- A patient who has an infection, fever, or has had an operation may require more insulin than usual.
- A patient who suffers from diarrhea or vomiting or who eats less than usual may require less insulin than usual.
- If the patient exercises more than usual or wants to change his/her usual diet, the insulin dose may need to be adjusted.
- A patient who is ill should be instructed to continue taking insulin, but the need for insulin may change.
- If a patient plans to travel over time zones, the need for insulin and the timing of injections may be affected. Patients should consult their doctor if they are planning such travel.
- If the patient is pregnant, planning to become pregnant, or is breastfeeding, she should contact her doctor for advice.
- If the patient drives or uses tools or machines, he/she should watch for signs of hypoglycemia. The patient's ability to concentrate or to react will be reduced during a hypoglycemic reaction. Patients should be instructed to keep this in mind in all situations where they might put themselves or others at risk (e.g., driving a car or operating machinery). Patients should never drive or use machinery if they feel a hypoglycemic reaction coming on. Patients should discuss with their doctor whether they should drive

Data from separate product monographs: comparative clinical significance has not been established

or use machines at all, if they have a lot of hypoglycemic reactions or if they find it hard to recognize hypoglycemia.

- Before patients travel, they should check with their doctor or pharmacist on the availability of their type and brand of insulin in other countries. If possible, the patient should bring enough insulin to last at least the length of the trip or longer.
- Thiazolidinediones used together with insulin may increase risk of edema and heart failure. Patients should inform their doctor as soon as possible if they experience localized swelling (edema) or signs of heart failure such as unusual shortness of breath.
- Hypokalemia is a possible side effect with all insulins. Patients might be more at risk if they are on potassium lowering drugs or losing potassium (e.g., diarrhea).

Inform patients about possible interactions with insulin.[21-30]

Many medications affect the way glucose works in the body, and this may influence insulin dose. Listed below are the most common medications that may affect insulin treatment. Patients should tell their doctor, nurse, or pharmacist if they are taking or have recently taken any other medications, including those obtained without a prescription. In particular, patients should tell their doctor or pharmacist if they are using any medication that affects blood glucose level.

The following medications may cause hypoglycemia: other diabetes medications, monoamine oxidase inhibitors (MAOIs), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, sulfonamides.

The following medications may cause hyperglycemia: oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, danazol.

Octreotide and lanreotide may either increase or decrease a patient's blood glucose level.

Beta-blockers may weaken or entirely suppress the first warning symptoms that help patients to recognize hypoglycemia.

Inform patients about side effects associated with insulins.

All insulins may cause hypoglycemia. The warning signs of hypoglycemia may come on suddenly and can include: cold sweat, cool pale skin, headache, rapid heartbeat, feeling sick, feeling very hungry, temporary changes in vision, drowsiness, unusual tiredness and weakness, nervousness or tremor, feeling anxious, feeling confused, and difficulty concentrating. Please see "Managing Hypoglycemia" section for information on how hypoglycemia should be treated.

Less commonly reported side effects (one to 10 users in 100):[21-30]

- Signs of allergy. Hives and rash may occur.
- Patients should seek medical advice immediately:
  - If the above signs of allergy appear or
  - If they suddenly feel unwell, and they start sweating, start being sick (vomiting), have difficulty breathing, have a rapid heartbeat, or feel dizzy.

Patients may have a very rare generalized serious allergic reaction to insulin or one of its ingredients.[21-30]

- **Lipodystrophy:** If patients inject themselves too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Rotating the site with each injection may help prevent such skin changes. If the patient notices the skin pitting or thickening at the injection site, he/she should tell the doctor or diabetes nurse educator, because these reactions can become more severe, or they may change the absorption of insulin at this site.
- **Diabetic retinopathy:** If a patient has diabetic retinopathy and his/her blood glucose levels increase very fast, the retinopathy may get worse.
- **Swollen joints:** When a patient starts taking insulin, water retention may cause swelling around the ankles and other joints. This soon disappears.
- **Painful neuropathy:** If blood glucose levels increase very quickly, it may cause burning, tingling, or electric pain. This is called acute painful neuropathy, and it usually disappears. If it does not disappear, the patient should see the doctor.
- **Vision problems:** When a patient first starts insulin treatment, it may disturb his/her vision, but the disturbance is usually temporary.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Insulins

Table 2: Availability of Insulins and Dosage Forms[21-30]	
Bolus (prandial) Insulins	
Rapid-acting insulin analogues (clear)	**Dosage Form Availability**
Insulin aspart and insulin aspart (faster acting)	10 mL vials, 3 mL cartridges, 3 mL disposable pens
Insulin glulisine	10 mL vials, 3 mL cartridges, 3 mL disposable pens
Insulin lispro	10 mL vials, 3 mL vials, 3 mL cartridges, 3 mL disposable pens
Short-acting insulin (clear)	**Dosage Form Availability**
Regular insulin	10 mL vials, 3 mL cartridges, 3 mL disposable pens
Insulin human biosynthetic 500 U/mL	3 mL disposable pen
Basal Insulins	
Intermediate-acting insulin (cloudy)	**Dosage Form Availability**
NPH Insulin	10 mL vials, 3 mL cartridges, 3 mL disposable pens
Long-acting insulin analogues (clear)	**Dosage Form Availability**
Insulin detemir	3 mL cartridges, 3 mL disposable pens
Insulin glargine 100 U/mL	10 mL vials, 3 mL cartridges, 3 mL disposable pens
Insulin glargine 300 U/mL	1.5 mL disposable pen
Insulin degludec 100 U/mL	3 mL disposable pen
Insulin degludec 200 U/mL	3 mL disposable pen
Premixed Insulins	
Premixed (regular/NPH) insulin (cloudy)	**Dosage Form Availability**
30/70, 40/60, 50/50 mix	10 mL vials (30/70 only), 3 mL cartridges (all), 3 mL disposable pens (30/70 only)
Premixed insulin analogues (cloudy)	**Dosage Form Availability**
Biphasic insulin aspart 30/70	3 mL cartridges, 3 mL disposable pens
Insulin lispro/insulin lispro protamine 25/75, 50/50	3 mL cartridges, 3 mL disposable pens

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Meglitinide
(Repaglinide)

* Pharmacists should refer to the most current product monographs for detailed information.

Note: The Forum for Injection Technique (FIT) guidelines provide best practice recommendations for insulin injection technique and can be found online at http://www.fit4diabetes.com/canada-english/

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for repaglinide.

Contraindications

Repaglinide is contraindicated in patients:[31]

- With diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
- With type 1 diabetes
- With severe liver disease
- Who are using gemfibrozil

Inform patients about possible warnings and precautions associated with repaglinide.

Before using repaglinide, patients should tell their doctor or pharmacist if they:[31]

- Have a history of liver or kidney problems
- Are pregnant or planning on becoming pregnant
- Are breastfeeding
- Are over 75 years of age
- Experience symptoms of hypoglycemia
- Suffer from fever, infection, surgery, or trauma (stress conditions) as it may cause hyperglycemia

Repaglinide has been reported to be associated with increased cardiovascular mortality (death) as compared to treatment with diet alone or diet plus insulin.

Pharmacological Options:
Meglitinide
(Repaglinide)

Inform patients about possible interactions with repaglinide.

Patients should talk with their doctor or pharmacist before taking any other medicine in addition to repaglinide, including over-the-counter products, as the following lists of interactions are not comprehensive.

Repaglinide

Use of repaglinide with gemfibrozil is contraindicated.

Before taking repaglinide, patients should tell their doctor or pharmacist if they are taking:[31]

- Monoamine oxidase inhibitors, beta blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, octreotide, non-steroidal anti-inflammatory agents (NSAIDs), anabolic steroids and corticosteroids, oral contraceptives, thiazides, danazol, thyroid hormones, sympathomimetics, clarithromycin, trimethoprim, rifampicin, itraconazole, ketoconazole, phenytoin, carbamazepine, phenobarbital, cyclosporine, deferasirox, decongestants, alcohol, grapefruit juice.

Inform patients about side effects associated with meglitinide.

Patients should talk with their doctor or pharmacist if they experience the following very common side effect with meglitinide:[31]

- Hypoglycemia

Patients should talk with their doctor or pharmacist if they experience the following common side effects with repaglinide:[31]

- Diarrhea, constipation, gas, nausea, abdominal pain or hyperglycemia

The following are uncommon side effects with repaglinide:[31]

- Liver dysfunction
- Allergy
- Itching

Patients should stop taking their medication and talk with their doctor or pharmacist if they experience any of the following serious side effects with repaglinide:[31]

- Sudden severe headache or worsening of headache, dizziness, fatigue or increased sweating

Patients should stop taking their medication and talk with their doctor or pharmacist if they experience any of the following uncommon serious side effects with repaglinide:[31]

- Sudden, partial, or complete loss of vision
- Chest pain or pressure and/or shortness of breath

This is not a complete list of side effects. For any unexpected effects while taking repaglinide, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Metformin

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for metformin.

Contraindications[32,33]

Metformin is contraindicated in individuals with the following circumstances:

- Unstable and/or type 1 diabetes
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma (Diabetic ketoacidosis should be treated with insulin.)
- In patients with a history of lactic acidosis, irrespective of precipitating factors
- In the presence of renal impairment or when renal function is not known; also in patients with serum creatinine levels above the upper limit of normal range
- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥136 µmol/L [males], ≥124 µmol/L [females] or abnormal creatinine clearance <60 mL/min), which may result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Excessive alcohol intake, acute or chronic
- Severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis (Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.)
- Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function
- Cardiovascular collapse and disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia
- During stress conditions, such as severe infections, trauma, or surgery and the recovery phase thereafter
- Severe dehydration
- Pregnancy or breastfeeding

Inform patients about possible warnings and precautions associated with metformin.

Serious Warnings and Precautions[32,33]

- Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment with metformin.
- Patients should be cautioned against excessive alcohol intake—either acute or chronic—when taking metformin, because alcohol intake potentiates the effect of metformin on lactate metabolism.

Before using metformin or metformin extended-release, patients should tell their doctor or pharmacist if they:[32,33]

- Have a history of kidney disease
- Are 80 years of age or older and have NOT had their kidney function tested
- Have liver disease
- Have metabolic acidosis (e.g., diabetic ketoacidosis)
- Have had a recent heart attack or stroke
- Have a serious infection
- Are dehydrated
- Are scheduled for surgery
- Are scheduled for x-ray or scanning procedures
- Are pregnant, breastfeeding, or planning to become pregnant
- Have a vitamin B_{12} or folic acid deficiency
- Drink alcohol

Metformin and metformin extended-release therapy may rarely be associated with lactic acidosis. Due to potential for lactic acidosis, patients should talk to their doctor if they take any form of metformin and:

- Develop or experience a worsening of heart disease, particularly heart failure
- Develop a serious medical condition, such as heart attack, severe infection, or a stroke

Data from separate product monographs: comparative clinical significance has not been established

Signs and symptoms of lactic acidosis include discomfort, muscle pain, difficult or fast breathing, extreme tiredness, weakness, upset stomach, stomach pain, feeling cold, low blood pressure, or slow or irregular heartbeat.

If any of the above side effects occur, the patient should contact their doctor immediately.

Inform patients about possible interactions with metformin.

Before taking metformin or metformin extended-release tablets, patients should tell their doctor or pharmacist if they are taking:[32,33]

- Other diabetes drugs, such as glyburide, insulin, and rosiglitazone
- Medications that may increase blood glucose levels such as diuretics, oral contraceptives, sympathomimetics, thyroid medicines, corticosteroids, phenytoin, nicotinic acid, or certain antihypertensives (e.g., calcium channel blockers)
- Isoniazid
- Furosemide
- Nifedipine
- Cationic drugs which may interfere with the elimination of metformin (e.g., cimetidine, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin)
- Coumarin-type anticoagulants
- Alcohol

Interactions with herbal products have not been established.

Inform patients about side effects associated with metformin.

Some common side effects of metformin products include diarrhea, nausea, and stomach upset. If they continue or are bothersome, the patient should check with his/her doctor.

After he/she is on the same dose for several days or weeks, if any of these symptoms come back, he/she should tell his/her doctor immediately. A late recurrence of stomach symptoms may be due to a serious medical condition (lactic acidosis).

The following serious side effects have been reported with the use of metformin:[32,33]

- *Uncommon (patient should stop taking medication and seek immediate medical attention):*[33] Lactic acidosis: Symptoms include being very weak or tired; having unusual (not normal) muscle pain; trouble breathing; stomach pain with nausea and vomiting or diarrhea; feeling cold, especially in arms and legs; feeling dizzy or lightheaded; having a slow or irregular heartbeat

This is not a complete list of side effects. For any unexpected effects while taking metformin products, patient should contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors
(Canagliflozin, Dapagliflozin, Empagliflozin)

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for canagliflozin, dapagliflozin, and empagliflozin.

Contraindications

Canagliflozin is contraindicated in:[34]

- Renally impaired patients with eGFR less than 45 mL/min/1.73 m^2, or end-stage renal disease, or patients on dialysis
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container

Dapagliflozin is contraindicated in:[35]

- Renally impaired patients with eGFR less than 60 mL/min/1.73 m^2, or end-stage renal disease, or patients on dialysis
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container

Empagliflozin is contraindicated in:[36]

- Renally impaired patients with eGFR less than 30 mL/min/1.73 m^2, severe renal impairment, end-stage renal disease and patients on dialysis
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container

Inform about possible warnings and precautions associated with SGLT2 inhibitors.

Before using canagliflozin, dapagliflozin, or empagliflozin, patients should talk to their doctor or pharmacist if they:[34,35]

- Have type 1 diabetes
- Are taking a diuretic, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) or have or have had hypotension
- Are older than 65 years of age
- Have or have had kidney problems
- Are taking antidiabetes medications such as glyburide, gliclazide or glimepiride (sulfonylureas) or insulin
- Have heart problems
- Have intolerance to some milk sugars (Canagliflozin and Dapagliflozin tablets contain lactose.)
- Are pregnant or are planning to become pregnant
- Are breastfeeding
- Are under 18 years of age

Also, before taking canagliflozin patients should talk to their doctor or pharmacist if they have liver problems.[34]

Also, before taking dapagliflozin patients should talk to their doctor or pharmacist if they have a history of bladder cancer.[35]

SGLT2 inhibitors will cause urine to test positive for glucose.[34,35]

Dapagliflozin use is associated with increased risk for fracture and amputation.

While a patient is taking SGLT2 inhibitors, the prescribing doctor may order a blood test to check the kidney function, blood fat levels (low-density lipoprotein cholesterol, or LDL-C) amount of red blood cells in the blood (haematocrit), and potassium blood levels.[34,35]

SGLT2 inhibitors may cause dizziness or lightheadedness. Patients should not drive or use machines until they know how the medication affects them.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors
(Canagliflozin, Dapagliflozin, Empagliflozin)

Inform patients about possible interactions with SGLT2 inhibitors.

Medications that may interact with canagliflozin include:[34]

- Digoxin, furosemide or other diuretics, ACE inhibitors, ARBs, insulin, sulfonylureas, carbamazepine, phenytoin, phenobarbital, efavirenz, ritonavir, rifampin, St. John's wort

Medications that may interact with dapagliflozin include:[35]

- Sulfonylureas, insulin, other antihyperglycemics, furosemide or other diuretics, bumetanide, valsartan, simvastatin, rifampin, digoxin and warfarin

Medications that may interact with empagliflozin include:[36]

- Sulfonylureas, insulin, other antihyperglycemics, furosemide or other diuretics

Inform patients about side effects associated with SGLT2 inhibitors.

Canagliflozin

Very common side effects (may affect more than one in 10 people):[34]

- Hypoglycemia when used with sulfonylurea or insulin
- Vaginal yeast infection (The symptoms include vaginal odour, white or yellowish vaginal discharge, and/or itching.)

Common side effects (may affect up to one in 10 people):[34]

- Rash or redness of the penis or foreskin (yeast infection or balanitis)
- Urinary tract infection
- Changes in urination, such as urinating more often or in larger amounts, an urgent need to urinate, and a need to urinate at night
- Constipation
- Nausea
- Feeling thirsty

Uncommon side effects (may affect up to 1 in 100 people):[34]

- Dehydration
- Rash
- Hives

The following side effects have been reported with the use of canagliflozin:[34]

- *Very Common (patients should contact their doctor or pharmacist in all cases):*
  - Vaginal yeast infection
- *Common (patients should contact their doctor or pharmacist in all cases):*
  - Rash or redness of the penis or foreskin
  - Urinary tract infection
- *Common (patients should contact their doctor or pharmacist only if severe):*
  - Constipation
- *Uncommon (patients should stop taking the drug and call their doctor or pharmacist in all cases):*
  - Dehydration
  - Fainting or lightheadedness with standing
  - Rash or hives
- *Rare (patients should contact their doctor or pharmacist in all cases):*
  - Severe hypoglycemia/disorientation/loss of consciousness/seizure (when used with insulin or a sulfonylurea)

This is not a complete list of side effects. For any unexpected effects while taking canagliflozin, patients should be informed to contact their doctor or pharmacist.

Dapagliflozin

The following side effects have been reported with use of dapagliflozin:[35]

- Sore throat
- Influenza
- Constipation
- Diarrhea
- Nausea
- Back pain
- Pain in the arms, legs, hands or feet
- Headache

Data from separate product monographs: comparative clinical significance has not been established

The following serious side effects have been reported with the use of dapagliflozin:[35]

- *Common (patients should contact their doctor or pharmacist in all cases):*
  - Urinary tract infection
- *Common (patients should contact their doctor or pharmacist only if severe):*
  - Yeast infection of the vagina or penis
- *Uncommon (patients should contact their doctor or pharmacist in all cases):*
  - Volume depletion (dehydration)
  - Hypotension
  - Hypoglycemia

This is not a complete list of side effects. For any unexpected effects while taking dapagliflozin, patients should be informed to contact their doctor or pharmacist.

Empagliflozin[36]

The following side effects have been reported with the use of empagliflozin:

- Dehydration, unusual thirst, passing more urine than usual or needing to pass more often, itching, staining or pain when emptying the bladder

The following serious side effects have been reported with the use of empagliflozin:

- *Very common (patients should contact their doctor or pharmacist in all cases):*
  - Hypoglycemia (shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood)
- *Common (patients should contact their doctor or pharmacist in all cases):*
  - Urinary tract infection
- *Common (patients should contact their doctor or pharmacist only if severe):*
  - Vaginal yeast infection, yeast infection of the penis
- *Common (patients should get immediate medical help):*
  - Volume depletion (dry mouth, headache, dizziness or urinating less often than normal)
- *Uncommon (patients should contact their doctor or pharmacist in all cases):*
  - Hypotension

This is not a complete list of side effects. For any unexpected effects while taking empagliflozin, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for sulfonylureas.

Contraindications

Gliclazide and gliclazide MR are contraindicated in patients with the following circumstances:[37,38]

- Known hypersensitivity or allergy to gliclazide, other sulfonylureas, sulfonamides, or to any of the excipients of this product
- Unstable and/or insulin-dependent diabetes mellitus, particularly type 1 diabetes; diabetic ketoacidosis; diabetic precoma and coma
- During stress conditions such as serious infection, trauma, or surgery
- In the presence of severe hepatic impairment
- In the presence of severe renal impairment
- Treatment with miconazole via systemic route or oromucosal
- Pregnancy and lactation

Glimepiride is contraindicated in patients with the following circumstances:[39]

- Type 1 diabetes
- Known hypersensitivity or allergy to glimepiride, other sulfonylureas, sulfonamides, or to any of the excipients of this product
- Diabetic ketoacidosis, with or without coma (This condition should be treated with insulin.)
- Pregnant or breastfeeding women
- In patients with severe impairment of renal or hepatic function, changeover to insulin is indicated to achieve optimal metabolic control

Pharmacological Options:
Sulfonylureas
(Gliclazide, Gliclazide MR, Glimepiride, Glyburide)

Glyburide is contraindicated in patients with the following circumstances:[40]

- Type 1 diabetes
- Known hypersensitivity or allergy to glyburide, any sulfonylurea or sulfonamides, any other component of the formulation
- Diabetic ketoacidosis, with or without coma (This condition should be treated with insulin.)
- Diabetic precoma or coma
- During stress conditions such as severe infections, trauma, or surgery
- In the presence of liver disease or frank jaundice or renal impairment
- If treated with bosentan
- Pregnancy and lactation

Inform patients about possible warnings and precautions associated with sulfonylureas.

All sulfonylureas may cause hypoglycemia. Patients should be aware of the symptoms associated with hypoglycemia and what to do should they experience symptoms.[37]

Before using a sulfonylurea, patients should tell their doctor or pharmacist if they: [37-40]

- Have or have had liver problems
- Have or have had kidney problems
- Have or have had heart condition (glimepiride and glyburide)
- Are pregnant or planning to get pregnant
- Are breastfeeding
- Have a blood disease called G6PD-deficiency anemia

Inform patients about possible interactions with sulfonylureas.

Patients should talk with their doctor or pharmacist before taking any other medicine in addition to sulfonylureas, including over-the-counter products, as the following lists of interactions are not comprehensive.

Gliclazide and gliclazide MR are contraindicated for use with miconazole.[37,38]

Drugs that may interact with gliclazide and gliclazide MR include:[37,38]

- Other antidiabetic agents, antibiotics (sulphonamides/sulfa drugs, clarithromycin), antituberculosis drugs, antifungal drugs (fluconazole), non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, salicylates, angiotensin converting enzyme (ACE) inhibitors, beta-blockers, anticoagulant therapy, diuretics, fibrates, nicotinic acid, H2-receptor antagonists, monoamine oxidase inhibitors, chlorpromazine, probenecid, salbutamol, terbutaline, ritodrine, barbiturates, oral contraceptives, danazol, alcohol.

The following interaction issues should be discussed with people taking glimepiride:[39]

- Patients should avoid drinking alcohol while taking this medicine.
- There are various drugs that can interact with glimepiride and cause hypoglycemia, which can be severe. Some of these drugs are acetylsalicylic acid, sulfonamides, warfarin, non-steroidal anti-inflammatory drugs (NSAIDs), some antibiotics (e.g., clarithromycin, tetracycline) and beta-blockers.
- Some medications increase difficulty in controlling blood glucose. These include diuretics, corticosteroids, ACE inhibitors, oral contraceptives, cold and allergy drugs.
- If taken at the same time, colesevelam reduces glimepiride absorption, which may result in hyperglycemia. Glimepiride should be taken at least four hours before colesevelam.

Drugs that may interact with glyburide include:[40]

- Diuretics, corticosteroids, ACE inhibitors, oral contraceptives, decongestants.
- Patients should avoid drinking alcohol while taking glyburide.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Sulfonylureas
(Gliclazide, Gliclazide MR, Glimepiride, Glyburide)

Inform patients about side effects associated with sulfonylureas.

Gliclazide and Gliclazide MR

Common side effects reported during clinical trials with gliclazide and gliclazide MR included:[37,38]

- Hypoglycemia, hyperglycemia, viral infection, upper respiratory infection, headache, high blood pressure, angina, leg swelling, diarrhea, constipation, abdominal pain, nausea, dizziness, skin rash/itching, depression, and back, muscle, and joint pain

The following serious side effects have been reported with the use of gliclazide and gliclazide MR:[37,38]

- *Common (patients should contact their doctor or pharmacist in all cases):*
  - Hypoglycemia
- *Uncommon (patients should stop taking medication and contact their doctor or pharmacist):*
  - Unexplained fever, chills, or sore throat
  - Yellowing of skin or eyes, dark-coloured urine, or light-coloured bowel movements (e.g., jaundice)
  - Skin rash, redness, itching, or hives
  - Chest pain or pressure, and/or shortness of breath
- *Uncommon (patients should talk with their doctor or pharmacist in all cases):*
  - Edema, swelling of the legs or unexpected weight gain
- *Very Rare (patients should stop taking medication and contact their doctor or pharmacist):*
  - Blood abnormalities with symptoms of sore throat, fever, mouth sore, unusual bleeding or bruising, anemia
  - Vasculitis
  - Hyponatremia
  - Angioedema (rapid swelling of tissues such as eyelids, face, lips, mouth, tongue, or throat that may result in breathing difficulty)
  - Widespread blistering or peeling of the skin

This is not a complete list of side effects. For any unexpected effects while taking gliclazide or gliclazide MR, patients should be informed to contact their doctor or pharmacist.

Glimepiride

Patients should talk with their doctor or pharmacist if they experience any of the following side effects with glimepiride:[39]

- Mild nausea or vomiting
- Dizziness
- Hypoglycemia
- A rash or sunburn secondary to exposure to sunlight or tanning bed (Patients should use a sunscreen when outdoors and avoid using sunlamps or tanning beds.)

Patients should call their doctor right away if they experience any of the following side effects:[39]

- Unexplained fever, chills, or sore throat
- Unusual bleeding or bruising
- Yellowing of skin or eyes, dark-coloured urine or light-coloured bowel movements
- Skin rash or hives
- Edema, swelling of the legs, or unexpected weight gain

Patients should stop taking the drug and seek medical help immediately if they have:[39]

- Severe allergic reactions (severe skin reaction; swelling of the throat, lips, tongue; difficulty breathing or swallowing)

This is not a complete list of side effects. For any unexpected effects while taking glimepiride, patients should be informed to contact their doctor or pharmacist.

Glyburide

The following side effects have been observed with glyburide use:[40]

- Nausea, heartburn, feeling "full," vomiting, diarrhea, and abdominal pain
- Allergic skin reactions (itchiness, rash, eruption) have been reported in a number of patients
- An increased sensitivity to light has been associated with the use of oral antidiabetic drugs
- Transient visual disturbances may occur at the beginning of the treatment due to variations in level of blood glucose

The following serious side effects have been reported with the use of glyburide:[40]

- *Common (patients should contact their doctor or pharmacist only if serious):*
  - Hypoglycemia
- *Uncommon (patients should contact their doctor or pharmacist in all cases):*
  - Skin reactions (itchiness, rash, eruption)
- *Rare (patients should contact their doctor or pharmacist in all cases):*
  - Blood disorders (unusual bruising or bleeding)
- *Very Rare (patients should stop taking drug and contact their doctor or pharmacist in all cases):*
  - Jaundice, angioedema (severe skin reaction, swelling of the throat, lips, tongue, difficulty breathing or swallowing)

This is not a complete list of side effects. For any unexpected effects while taking glyburide, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Ensure that therapy is right for your patient.

Please see Table 1 for indications and associated doses for TZDs.

Contraindications

Pioglitazone is contraindicated in:[41]

- New York Heart Association (NYHA) Class I to IV cardiac status
- Serious hepatic impairment
- Pregnancy (Insulin is recommended during pregnancy to control blood glucose levels, oral antidiabetic agents should not be given.)
- Active bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic hematuria

Rosiglitazone is contraindicated in:[42]

- New York Heart Association (NYHA) Class I to IV cardiac status
- Serious hepatic impairment
- Pregnancy (Insulin is recommended during pregnancy to control blood glucose levels, oral antidiabetic agents should not be given.)

Inform about possible warnings and precautions associated with TZDs.

Pioglitazone

Serious side effects with pioglitazone include:[41]

- Heart failure (Symptoms of heart failure include shortness of breath, weakness, tiredness, edema, or unusual weight gain.)
- Liver problems (Symptoms of liver problems include tiredness, lack of appetite, dark urine, yellowing of the skin or the white part of the eye.)
- Bladder cancer (Symptoms of bladder cancer include blood or a red colour in the urine, an increased need to urinate, or pain during urination.)

Pharmacological Options:
Thiazolidinediones (TZDs)
(Pioglitazone, Rosiglitazone)

Following are additional warnings and precautions associated with use of pioglitazone:[41]

- Pioglitazone is not approved for use with metformin and a sulfonylurea.
- Pioglitazone is not approved for use with insulin therapy.
- Taking pioglitazone with a sulfonylurea may cause hypoglycemia.
- Patients should consult their doctor promptly during periods of stress, such as fever, trauma, infection or surgery, since medication requirements may change during these times.
- Fractures—usually in the hand, upper arm or foot—have been seen with pioglitazone use in women.

Patients should talk to their doctor or pharmacist before or while taking pioglitazone if they:[41]

- Have liver disease (Pioglitazone is not recommended in patients with liver disease.)
- Are planning to become pregnant (Only insulin should be used during pregnancy to maintain blood glucose levels as close to normal as possible.)
- Are breastfeeding
- Are women who have not reached menopause but have no menstrual periods (A woman may become pregnant unless she uses an effective method of birth control. Pioglitazone, like other drugs in this class, may cause women with insulin resistance to ovulate again.)
- Have edema

Rosiglitazone

Serious Warnings and Precautions[42]

- Rosiglitazone, like other thiazolidinediones, can cause fluid retention and congestive heart failure.
- Rosiglitazone may be associated with an increased risk of cardiac ischemia. **Rosiglitazone is not recommended in patients with a history of ischemic heart disease, particularly those with myocardial ischemic symptoms.**
- Rosiglitazone should be used only when all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance.

Before using rosiglitazone, patients should talk to their doctor or pharmacist about all their medical conditions, if:[42]

- They have experienced edema (swelling in the wrists, hands, feet or ankles).
- They have been diagnosed with angina or have had a myocardial infarction.
- They have heart-related risks, including cigarette smoking, high blood pressure, high cholesterol, or a family history of heart attack.
- They are taking nitrate medicines.
- They have macular edema.
- They have liver problems.
- They are breastfeeding.
- They are pregnant or planning to become pregnant.
- They have not reached menopause but have no menstrual periods—e.g., polycystic ovary syndrome. Rosiglitazone may cause patients to ovulate again, which means they could get pregnant. Patients should discuss effective contraception methods with their health professional.
- They have suffered broken bones, usually in the hand, upper arm or foot.
- They have decreases in spine and hip bone mineral density.
- They have muscle problems, including muscle tenderness, weakness, or pain that they cannot explain.
- They have experienced brownish or discoloured urine with muscle problems. If this is the case, patients should stop taking rosiglitazone and call their doctor right away.
- Under the age of 18.

Rosiglitazone is not recommended for type 1 diabetes or diabetic ketoacidosis.

Rosiglitazone is not approved for use with metformin and a sulfonylurea.

Rosiglitazone is not approved for use with insulin therapy.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Thiazolidinediones (TZDs)
(Pioglitazone, Rosiglitazone)

Inform patients about possible interactions with TZDs.

Drugs that interact with pioglitazone include:[41]

- Oral contraceptives: Women using oral contraceptives should check with their doctor about the possible need to adjust the dose or use alternative methods of contraception when taking pioglitazone. Women should also inform their doctors of any changes in their monthly cycle.
- Pioglitazone may also interact with some other drugs such as gemfibrozil, rifampin, nifedipine, and atorvastatin calcium.

Drugs that may interact with rosiglitazone include:[42]

- Gemfibrozil, rifampin, methotrexate

Inform patients about side effects associated with TZDs.

Pioglitazone

The following side effects have been commonly reported with pioglitazone (could affect up to one in 10 patients):[41]

- Edema (fluid retention or swelling), which could lead to heart failure
- Hypoglycemia (if pioglitazone taken in combination with metformin or a sulfonylurea)
- Increased weight (Patients should tell their doctor if they have gained a lot of weight in a short period of time.)

The following side effects have been reported rarely with pioglitazone (could affect up to 1 in 1,000 patients):[41]

- Liver problems
- Breakthrough bleeding while using oral contraceptives, or in general
- Blurred vision due to swelling in the back of the eye
- Fractures, usually in the hand, upper arm or foot, have been seen with pioglitazone use in women
- Bladder cancer

The following side effects have been reported very rarely with pioglitazone (could affect up to 1 in 10,000 patients):[41]

- Heart failure or pulmonary edema
- Anemia
- Angioedema (swelling of the face, lips, mouth, tongue, or throat that may cause difficulty in swallowing or breathing; hives or rash that may be itchy)

The following serious side effects have been reported with the use of pioglitazone:[41]

- *Common (patients should contact their doctor in all cases):* fluid retention or swelling in extremities
- *Common when taken with other antidiabetic medications (patients should contact their doctor only if severe):* hypoglycemia
- *Rare (patients should stop taking pioglitazone and contact their doctor immediately):*
  - Liver problems: nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine, or yellowing of skin
  - Blurred vision or decreased vision
  - Bladder cancer: blood or red colour in urine, increased need to urinate, pain while urinating
- *Rare (patients should contact their doctor in all cases):* Fractures, usually in the hand, upper arm or foot, in women
- *Very Rare (patients should stop taking pioglitazone and contact their doctor immediately):* Heart failure or fluid in the lungs (pulmonary edema): trouble breathing or shortness of breath, getting tired easily after light physical activity, unusual tiredness, waking up short of breath at night, swollen ankles or feet, unusually rapid increase in weight
- *Very Rare (patients should stop taking pioglitazone and contact their doctor immediately):* Angioedema (swelling of the face, lips, mouth, tongue, or throat that may cause difficulty in swallowing or breathing; hives or rash that may be itchy)

This is not a complete list of side effects. For any unexpected effects while taking pioglitazone, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Pharmacological Options:
Thiazolidinediones (TZDs)
(Pioglitazone, Rosiglitazone)

Rosiglitazone

Common side effects (could affect up to one in 10 people):[42]

- Anemia
- Angina
- Heart failure or pulmonary edema
- Edema, which could lead to or worsen heart failure
- Broken bones, usually in the hand, upper arm, or foot
- A small increase in total cholesterol levels
- Hypoglycemia (if taking rosiglitazone in combination with other antidiabetes medications)
- Increased weight (Patients should tell their doctor if they gain a lot of weight in a short period of time.)

Uncommon side effects (could affect up to 1 in 100 people):

- Heart failure or pulmonary edema
- Constipation
- Increased hunger

Rare side effects (could affect up to 1 in 1,000 people):

- Liver problems
- Blurred vision due to swelling in the back of the eye

Very rare side effects (could affect up to 1 in 10,000 people):

- Allergic reactions, which may include hives or rash (possibly itchy), or more serious symptoms that may occur suddenly, such as swelling of the face, lips, mouth, tongue, or throat that may cause difficulty in swallowing or breathing
- Breakthrough bleeding while using oral contraceptives, or in general
- Muscle problems (If patients experience muscle tenderness, weakness, or pain that they cannot explain, they should talk with their doctor. If they experience brownish or discoloured urine with muscle problems, they should stop taking rosiglitazone and call their doctor right away.)
- Patients may experience swelling of the parotid gland (salivary glands located over the jaw, in front of the ears)

The following serious side effects have been reported with the use of rosiglitazone:[42]

- *Common (patients should contact their doctor in all cases):*
  - Fluid retention or swelling in extremities
  - Anemia
  - Angina
- *Common when taken with other antidiabetic medications (patients should contact their doctor only if severe):* hypoglycemia
- *Common when taken with a sulfonylurea or metformin or uncommon when rosiglitazone is taken alone (patients should stop taking rosiglitazone and call their doctor immediately):* Heart failure or fluid in the lungs (pulmonary edema): trouble breathing or shortness of breath, getting tired easily after light physical activity, unusual tiredness, waking up short of breath at night, swollen ankles or feet, unusually rapid increase in weight
- *Rare (patients should stop taking rosiglitazone and contact their doctor immediately):*
  - Liver problems: nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine, or yellowing of skin
  - Blurred vision or decreased vision
  - Brownish or discoloured urine
- *Very Rare (patients should stop taking rosiglitazone and contact their doctor immediately):* Angioedema–hives or rash (possibly itchy) or more serious symptoms that may occur suddenly, such as swelling of the face, lips, mouth, tongue, or throat that may cause difficulty in swallowing or breathing
- *Very Rare (patients should contact their doctor in all cases):*
  - Muscle tenderness or weakness, muscle pain that cannot be explained
  - Generalized weakness, especially if patient does not feel well

This is not a complete list of side effects. For any unexpected effects while taking rosiglitazone, patients should be informed to contact their doctor or pharmacist.

Data from separate product monographs: comparative clinical significance has not been established

Managing Hypoglycemia

Managing Hypoglycemia

Hypoglycemia is defined by:[43]

1) The development of autonomic or neuroglycopenic symptoms
2) A low plasma glucose level (<4.0 mmol/L for patients treated with insulin or an insulin secretagogue) and
3) Symptoms responding to the administration of carbohydrate.

The severity of hypoglycemia is defined by clinical manifestations.

Hypoglycemia can be severe and result in confusion, coma, or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. It is important to prevent, recognize, and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues.[43]

Symptoms[43]

- Neurogenic (autonomic) symptoms of hypoglycemia include trembling, palpitations, sweating, anxiety, hunger, nausea, and tingling
- Neuroglycopenic symptoms of hypoglycemia include difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness

Severity of hypoglycemia is classified as follows:[43]

Mild: Autonomic symptoms are present. The individual is able to self-treat.

Moderate: Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.

Severe: The individual requires assistance of another person. Unconsciousness may occur. Plasma glucose is typically < 2.8 mmol/L.

Treatment is recommended by the Canadian Diabetes Association as follows:[43]

Mild to moderate hypoglycemia in adults: Treated by the oral ingestion of 15 g carbohydrate, preferably as glucose or sucrose tablets or solution (preferable to orange juice and glucose gels). Blood glucose should be retested in 15 minutes; if blood glucose level remains < 4.0 mmol/L, it should be re-treated with a further 15 g carbohydrate.

Severe hypoglycemia in conscious adults: Treated by oral ingestion of 20 g carbohydrate, preferably as glucose tablets or equivalent. Blood glucose should be retested in 15 minutes and then re-treated with another 15 g glucose if the blood glucose level remains < 4.0 mmol/L.

Once the hypoglycemia has been reversed: the person should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia. If a meal is >1 hour away, a snack (including 15 g carbohydrate and a protein source) should be consumed.

Examples of 15 g carbohydrate include:[43]

- 15 g glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water
- 175 mL (3/4 cup) of juice or regular soft drink
- 6 Life Savers® (1 = 2.5 g carbohydrate)
- 15 mL (1 tablespoon) honey

See 2018 Diabetes Canada Guidelines at *http://guidelines.diabetes.ca/Browse/Chapter14* for treatment of severe hypoglycemia in an unconscious individual.[43]

For treatment options in children, see "Type 1 Diabetes in Children and Adolescents" in 2018 Diabetes Canada Guidelines at *http://guidelines.diabetes.ca/Browse/Chapter34*.

For Your Patients Who Experience Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (*http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php*);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (*http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php*).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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25. Novolin® ge NPH (insulin isophane human biosynthetic) Product Monograph.
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27. Lantus® (insulin glargine) Product Monograph.
28. Tresiba® (insulin degludec) Product Monograph.
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CE Questions

Submitting Answers to the CE Questions

1. Create an account at www.healthelearning.ca if you do not already have one.
2. Log in to your Pear Health eLearning account and click CE COURSES.
3. Select "Diabetes: Pharmacological Options and Considerations for Management Guide," then click ENROL NOW.
4. Follow the onscreen prompts to complete the order.
5. Click MY ACCOUNT/ENROLLED COURSES.
6. Enter the CE and select the answers to the CE Test, then click SUBMIT.

Note:

You must correctly answer seven out of 10 (70%) in order to obtain 1.0 CE unit.
You may make two attempts to achieve a passing grade.

If you achieve 70% or more on your first attempt, your test results and Letter of Completion will be emailed to you for your personal records. You can access this document under MY ACCOUNT/COMPLETED COURSES.

Case 1: Gerry is a 43-year-old man who was told by his doctor two years ago that he had prediabetes. Gerry was informed that he should see a dietitian to talk about his diet and start engaging in more physical activity. Unfortunately, Gerry did not change his lifestyle significantly and he has just been diagnosed with type 2 diabetes, with a hemoglobin A1C (A1C) of 8.0%.

1. According to the 2018 Diabetes Canada Guidelines, which of the following drugs should Gerry be started on?

a. A sulfonylurea
b. Metformin
c. Acarbose
d. Any two of the above

2. Gerry is taking a statin to control cholesterol and an ACE inhibitor to reduce blood pressure and prevent vascular disease. Which of the following would be the most appropriate A1C target for Gerry?

a. ≤ 6.5%
b. ≤ 7.0%
c. ≤ 7.5%
d. 7.1-8.5%

3. Gerry is asking you if he should get a blood glucose meter. Which of the following statements is TRUE?

a. People with type 2 diabetes should monitor their blood glucose at least twice a day regardless of circumstances
b. Blood glucose monitoring should be conducted before a meal, after a meal and at bedtime each day for people with type 2 diabetes
c. Evidence for benefit of blood glucose monitoring in type 2 diabetes is strongest for the first six months after diagnosis
d. Blood glucose monitoring should only be conducted in people with type 2 diabetes who use insulin

4. Gerry has decided to start working again on his nutrition and physical activity goals. Which of the following statements is TRUE?

a. Nutrition therapy can reduce A1C level by up to 2%
b. Physical activity benefits include cardiorespiratory fitness and improved lipid profile, but not glycemic control
c. Weight loss of 15% is required to substantially improve glycemic control
d. All of the above statements are true

Case 2: Sylvia is a 62-year-old woman who has been taking metformin for six years. Her A1C has been 7.8% over the past 6 months and her doctor would like to add a drug to her regimen. Sylvia is currently taking ramipril-hydrochlorothiazide 10/25 mg once daily, rosuvastatin 40 mg once daily, enteric coated ASA 81 mg once daily, metformin 500 mg three times daily. Sylvia has had a stent placed in the past and carries nitroglycerin spray with her in case of angina. Sylvia's eGFR is 69 mL/min/1.73m^2.

5. Sylvia is overweight and does not want a drug that might cause weight gain. Which of the following would be the most appropriate choice to add to metformin?

a. Glyburide
b. Rosiglitazone
c. Basal insulin
d. Alogliptin

6. Sylvia tells you that she has heard about a new drug that works by "getting rid of sugar through the urine." You realize she is talking about SGLT2 inhibitors. You explain to Sylvia that an SGLT2 inhibitor would probably not be the right choice for her. Which of the following explains your rationale?

a. She is at increased risk for a vaginal yeast infection
b. SGLT2 inhibitors interact with metformin
c. Her kidney function is too low to use an SGLT2 inhibitor
d. It is not advisable to use an SGLT2 inhibitor with a diuretic

7. Although she has never had an issue, Sylvia is concerned about hypoglycemia because she will be taking a second antihyperglycemic medication. You are educating Sylvia on the symptoms of hypoglycemia. Which of the following would be classified as a "mild" hypoglycemic symptom combination that the patient could self-treat?

a. Sweating and nausea
b. Sweating, headache and drowsiness
c. Vision changes, trembling and palpitations
d. Dizziness, tingling and weakness

Case 3: Conrad is 11 years old and has recently been diagnosed with type 1 diabetes. His mother is in the pharmacy with him and visibly anxious about Conrad's medical condition. You invite Conrad and his mother into your counselling room to discuss issues around managing type 1 diabetes.

8. Conrad's mother asks about blood glucose monitoring. How many times a day should a person with type 1 diabetes monitor blood glucose?

a. Twice a day, before breakfast and supper and more often if blood glucose is not controlled
b. At least three times a day
c. Before breakfast and at bedtime, and more often if blood glucose is not controlled
d. At least once a day, but at a different time each day (e.g., before a meal, after a meal, at bedtime).

9. Conrad will be using a rapid-acting insulin analogue and a long-acting basal insulin analogue for treatment. Which of the following rapid-acting insulin analogues should be used no more than 5 to 10 minutes before a meal?

a. Insulin aspart
b. Insulin glulisine
c. Insulin lispro
d. All of the above

10. Conrad will be using insulin glargine as the basal insulin. When is the best time to inject insulin glargine?

a. At bedtime
b. First thing in the morning
c. After dinner
d. Any time, but same time every day

Notes

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