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YOUR MEDICATION INFORMATION SERVICE

Ozempic for Treatment of Diabetes

DRUG SHORTAGE

Ozempic is supplied in pre-filled pens delivering doses of 0.25 mg/0.5 mg or 1 mg. Both formats are in short supply due to global supply constraints and increased demand. Supply is available intermittently but is unpredictable, insufficient to meet current demand, and is not expected to stabilize until at least **March 31, 2024**.[1]

Healthcare providers are encouraged to discuss this with patients and incorporate shared decision making on potential options: continuing with available supply, switching to an alternative antihyperglycemic agent, or discontinuing.

A Quick Guide and other resources are available on our website.

Contents

Continue Ozempic with Available Supply

Use a lower dose

- Depending on pen size availability, using lower doses regularly may be achievable and allow for consistent concentrations.
- **Blood glucose and weight can be expected to increase with lower dose; however, the reduction in MACE was similar between doses of 0.5 mg and 1 mg semaglutide subcut once weekly in SUSTAIN-6.**[2]
- **Ensure the patient understands the possibility of complete disruption in supply** and that this strategy may simply delay the need to switch to another antihyperglycemic agent. Take this opportunity to plan.

Use Ozempic intermittently or extend dosing interval

- Use as availability allows, meaning doses may be missed/ dosing intervals extended.
- To preserve supply as much as possible[1]:
  - Limit refills to 30-day supplies.
  - Encourage patients to contact pharmacy or health care provider before current supply runs out.
  - While effects on blood glucose and weight can be monitored, it is unknown how missed doses/extended intervals affect cardiorenal benefit.
- Extended intervals between doses may increase the risk for gastrointestinal side effects at next dose.[3] Consider returning to a starting dose and re-titrating if three or more doses have been missed.

Discontinue Ozempic and Switch to Another Agent

While it may be desirable to switch to an agent with GLP-1 agonist activity, these agents may be inaccessible to many patients due to cost, lack of formulary coverage, and potential supply issues. Consider switching to an antihyperglycemic agent with a different mechanism of action until supply of Ozempic stabilizes.

Switch to Antihyperglycemic Agent from a Different Class

- Review antihyperglycemic therapy history.
  - As metformin is a first-line agent on account of its safety, cardiovascular benefit, weight loss (or weight neutral) effects, and low cost, take this time to investigate reasons why metformin is not on board or is at submaximal dose.[4]
    - A common reason is gastrointestinal intolerance, which may have resulted from aggressive dose titration. Consider if metformin can be re-initiated (or the dose increased) using a slower titration (increase daily dose by 250-500 mg every 2 to 4 weeks).[4,5]
  - If semaglutide replaced an antihyperglycemic that was well-tolerated with reasonable effectiveness, consider returning to that agent.
- Add a new agent. Base decision on:
  - Duration of type 2 diabetes (longer duration often indicates inadequate endogenous insulin production and need to start basal insulin +/- prandial insulin).
  - Cost, drug coverage—alternatives may only be on formulary as Exception Drug Status/Limited Use Benefit, or may not be covered at all.
  - Comorbidities—pay special attention to cardiovascular disease and renal disease.[6,7]
    - **SGLT-2 inhibitors benefit for:** MACE (canagliflozin, empagliflozin); heart failure (all); diabetic kidney disease (all)
    - **Metformin potential benefit** for MACE and heart failure
    - **TZD: potential benefit** for MACE (pioglitazone); **potential harm for heart failure** (pioglitazone/ rosiglitazone)
    - In general, benefits have been demonstrated in high-risk patients.
  - Outcomes—relative reductions of A1C and weight
    - A1C lowering[8]: insulin, GIP-GLP-1 agonist > GLP-1 agonist, metformin, SU > repaglinide, TZD > SGLT-2 inhibitor, DPP-4 inhibitor

    - Weight[6,7]
        - reduction: GIP-GLP-1 agonist > GLP-1 agonist > SGLT-2 inhibitor > metformin (or neutral)
        - neutral: DPP-4 inhibitor
        - gain: insulin, TZD > repaglinide, SU
    - Adverse effects
    - Drug interactions
    - Pharmacotherapy regimen—likelihood for adherence, oral vs. injectable, storage, convenience
    - Patient preference
    - See the RxFiles Outcomes Comparison Summary Table[7] for comparisons of these factors.
- The following agents do not have the same degree of glucose lowering and weight loss as Ozempic, but may be good candidates during the shortage[3]:
    - SGTL-2 inhibitors, especially if established or high-risk for cardiorenal disease
    - DPP-4 inhibitors as they have similar mechanism of action and may control postprandial hyperglycemia
    - Basal (+/- prandial) insulin, especially if glycemic control is a concern
- **Choose dose** based on: current glycemic control, renal function, and drug interactions.
    - In general, beginning with the starting dose is prudent and allows for use of lowest effective dose.
- **Start the new agent seven days after the last dose of Ozempic** (i.e., at the time of the next scheduled Ozempic dose).

Switch to Oral Semaglutide

- Oral semaglutide decreases A1C by approximately 1–1.5% (similar to Ozempic).[5,9]
- Unlike Ozempic, oral semaglutide—at doses used for diabetes—has not been shown to reduce the risk of MACE. Oral semaglutide may reduce mortality, though this was only seen in exploratory endpoints and statistical significance cannot be determined.[10]
- **Oral semaglutide is taken daily on an empty stomach upon waking, with only minimal water and no other food, drink, or medications for at least 30 minutes to ensure maximal absorption.[11]**

Switch to Alternative Subcut GLP-1 Agonist

- **Dulaglutide** and **liraglutide** decrease A1C by approximately 1–1.5% (similar to Ozempic).[5,9]
- Dulaglutide and liraglutide reduce MACE; liraglutide also reduces cardiovascular and all cause mortality.[12,13]
- Injectable GLP-1 agonists are administered subcut either daily (liraglutide) or weekly (dulaglutide) without regard to meals.[14,15]
- Lixisenatide is a short-acting GLP-1 agonist with no evidence of cardiovascular benefit.[16] This GLP-1 agonist is no longer available as a single entity; it is only available in combination with insulin glargine.[17] Lixisenatide/insulin glargine is the only basal insulin GLP-1 agonist combination product on formularies and may obviate the need for prandial insulin.

How to Switch from Ozempic Once Weekly to Other GLP-1 Agonists

- There are no direct conversions or dose equivalents when switching between different GLP-1 agonists.
- Dose equivalents have been approximated in the literature based on clinical experience of authors and doses used in head-to-head trials (Table 1).[3,18]
    - It is recommended to **use the approximated equivalent dose of the new GLP-1 agonist as a starting point**. Also consider length of time without Ozempic and how Ozempic was originally tolerated when choosing dose.[3,18]
        - Adjust initial dose as needed based on side effects and glycemic control; titrate as tolerated and needed.
        - Similar glycemic control may not be achieved if switching to other GLP-1 agonists; be prepared to add other antihyperglycemic agents.
- **Administer the first dose of the new GLP-1 agonist seven days after the last dose of Ozempic.[18] Oral semaglutide may be started within seven days of the last dose of Ozempic.[19]**

Table 1: GLP-1 Agonists

Drug/Cost*/ Formulary Status	Dosage¥/ Approximate Equivalent Dose[3,18]	Supplied As	Storage
semaglutide Ozempic[20] ~$230[9] SPD[21]: EDS† NIHB[22]: Open benefit	Initial: 0.25 mg subcut once weekly for 4 weeks. Increase to 0.5 mg subcut once weekly. May increase as needed to 1-2 mg subcut once weekly at intervals no shorter than 4 weeks.	Multidose pre-filled pen 2 mg pen: delivers 0.25 or 0.5 mg per dose (0.68 mg/mL x 3 mL or 1.34 mg/mL x 1.5 mL) 4 mg pen: delivers 1 mg per dose (1.34 mg/mL x 3 mL) 8 mg pen^: delivers 2 mg per dose (2.68 mg/mL x 3 ml) Cartons of 1 pen	Keep refrigerated (2°C to 8°C) until expiry date. After initial use, store at 2°C to 30°C for up to 8 weeks. Remove injection needle and store with pen cap on.
semaglutide Rybelsus[11] ~$230[9] SPD[21]: Not a benefit NIHB[22]: Not a benefit	Initial: 3 mg PO once daily. Increase to 7 mg PO once daily after 30 days. May increase to 14 mg PO once daily after a further 30 days. semaglutide 14 mg PO once daily ~ semaglutide 0.5 mg subcut once weekly	Oral tablet 3 mg, 7 mg, 14 mg Blister pack sizes of 30, 60, 90 tablets	Store at 15°C to 30°C until expiry date.
dulaglutide Trulicity[15] ~$230[9] SPD[21]: Not a benefit NIHB[22]: Not a benefit	Initial: 0.75 mg subcut once weekly for 4 weeks. Increase to 1.5 mg subcut once weekly thereafter. May increase as needed to 3-4.5 mg subcut once weekly at intervals no shorter than 4 weeks. dulaglutide 1.5 mg subcut once weekly ~ semaglutide 0.5 mg subcut once weekly; see *Supplied As*	Single-dose pre-filled pen 0.75 mg/0.5 mL 1.5 mg/0.5 mL 3 mg/0.5 mL^ 4.5 mg/0.5 mL^ Packs of 4 pens Because the higher strength pens are not available in Canada, it is reasonable to switch semaglutide 0.5 mg to dulaglutide 0.75 mg once weekly and switch semaglutide 1 mg (or higher) to dulaglutide 1.5 mg once weekly.	Keep refrigerated (2°C to 8°C) until expiry date. May be stored at room temperature (up to 30°C) for up to 14 days.
liraglutide Victoza[14] ~$220[9] SPD[21]: Not a benefit NIHB[22]: Not a benefit	Initial: 0.6 mg subcut once daily for 1 week. Increase to 1.2 mg subcut once daily. May increase to 1.8 mg subut once daily after one further week. liraglutide 1.8 mg subcut once daily ~ semaglutide 0.5 mg subcut once weekly	Multidose pre-filled pen 18 mg pen: delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL x 3 mL) Packs of 2 or 3 pens	Keep refrigerated (2°C to 8°C) until expiry date. After initial use, store at 2°C to 30°C for up to 30 days. Remove injection needle and store with pen cap on.
Combination Products[17]			
liraglutide/ insulin degludec Xultophy Not a benefit of SPD[21] or NIHB[22]		*lixisenatide/insulin glargine* Soliqua SPD[21]: EDS‡; NIHB[22]: open benefit	

*Cost of 30-day supply; includes drug cost only.

¥ See product monographs or Diabetes Canada[23] for dosing/precautions in those with chronic kidney disease.

† For the treatment of type 2 diabetes in combination with metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.

^ Approved in Canada but not marketed.

‡ For treatment of type 2 diabetes in patients on a basal insulin (> 30 units/day) with or without metformin, in patients who have been uncontrolled on, or are intolerant to, a sulfonylurea and metformin.

EDS=Exception Drug Status; **SPD**=Saskatchewan Drug Plan; **NIHB**=Non-Insured Health Benefits; **PO**=by mouth; **subcut**=subcutaneous

Switch to GIP-GLP-1 Agonist

- Tirzepatide (Mounjaro) is the first agent in this novel class of antihyperglycemic agents that has activity at both the GIP and GLP-1 receptors.
- GIP and GLP-1 are both incretins as they stimulate insulin release from beta cells.[24]
- The dose is administered subcut once weekly without regard to meals.[25]
  - No dose adjustment is required in renal impairment, though experience is very limited in those with eGFR < 30 mL/min/1.73m^2.
- A paper describing an adjusted indirect treatment comparison method suggests semaglutide 2 mg subcut once weekly has similar effect on A1C as tirzepatide 5 mg subcut once weekly.[26]
  - Based on this data and clinical judgment, it has been suggested to consider[3]:
    - semaglutide 0.5 mg subcut once weekly approximately equivalent to tirzepatide 2.5 mg subcut once weekly
    - semaglutide 1 mg subcut once weekly approximately equivalent to tirzepatide 2.5 mg—5 mg subcut once weekly.
  - **It is reasonable that all patients are switched to tirzepatide 2.5 mg subcut once weekly, the starting dose, and titrated accordingly** (Table 2).
- There is some limited data of cardiovascular safety of tirzepatide (5 to 15 mg) compared to insulin glargine.[27] While studies are underway,[28,29] it is not known if tirzepatide confers cardiorenal benefit.

Table 2: GIP-GLP-1 Agonists

Drug/Cost*/ Formulary Status	Dosage	Supplied As	Storage
tirzepatide Mounjaro $320[30] SPD[21]: Not a benefit NIHB[22]: Under review	Initial: 2.5 mg subcut once weekly. Increase to 5 mg subcut once weekly after 4 weeks. Increase as needed up to 15 mg subcut once weekly in 2.5 mg/week increments at intervals no shorter than 4 weeks.	Single-dose vial Single-dose pre-filled pen^ 2.5 mg/0.5 mL 5 mg/0.5 mL 7.5 mg/0.5 mL 10 mg/0.5 mL 12.5 mg/0.5 mL 15 mg /0.5 mL Individual vials	Keep refrigerated (2°C to 8°C) until expiry date. Vials may be stored at room temperature (up to 30°C) for up to 21 days.

*Cost of 30-day supply; includes drug cost only.

^ Approved in Canada but not marketed.

SPD = Saskatchewan Drug Plan; NIHB = Non-Insured Health Benefits; subcut = subcutaneous

Discontinue Ozempic

- Consider if GLP-1 agonist therapy is required.
  - It may be possible to discontinue Ozempic and maintain goals if glycemic control is well below target, if the patient has had significant weight loss and is able to maintain lifestyle management, and/or if glycemic targets can be relaxed (e.g., patient has become frail since starting).
    - Unless A1C is only marginally elevated, most patients will require additional pharmacotherapy to maintain goals after discontinuing an effective agent.
- Optimize doses of current agents, recognizing this is often not feasible because:
  - Additional benefit (e.g., A1C lowering, cardiorenal) is not always linear across dose ranges and increased doses may not achieve greater benefit. This is especially true with SGLT-2 inhibitors.
  - Increasing doses may tip the balance to greater harm, especially agents associated with hypoglycemia.
  - There may be room for insulin doses to be increased but avoid overbasalization (> 0.5 units/kg/day). Overbasalization occurs when basal insulin is increased in the setting of controlled fasting glucose yet persistent postprandial hyperglycemia, leading to risk of hypoglycemia and uncontrolled A1C. Prandial insulin (with largest meal or more frequently) is usually required to control postprandial hyperglycemia.[31]

Monitoring

- Glycemic targets[32]
  - A1C: every 3 months with therapy adjustment/change
  - Self-monitoring of blood glucose: 1 or 2 times per week; increase frequency if using insulin, experiencing signs/symptoms of hypoglycemia, and/or during illness
- Serum creatinine, eGFR[5]
  - SGLT-2 inhibitors: serum creatinine increase expected on initiation (up to 25-30%); reassess if >30%. Obtain baseline, repeat 2 to 4 weeks after initiation, then periodically.
  - Other agents: baseline and periodically
- Liver function tests[5]
  - Repaglinide, SUs, TZDs—baseline and periodically
  - DPP-4 inhibitors—baseline
- Volume status, blood pressure[5]
  - SGLT-2 inhibitors: periodically; monitor for hypovolemia, hypotension
- Electrolytes[5]
  - SGLT-2 inhibitors: within 2-4 weeks of initiation, then periodically; monitor for hypovolemia, renal function (K+)
- Adverse effects[9]
  - Metformin: nausea, diarrhea, abdominal discomfort, anorexia, metallic taste, lactic acidosis if hepatic or renal disease, vitamin B12 deficiency with long-term use
  - DPP-4 inhibitors: nasopharyngitis, hypersensitivity reactions, pancreatitis (rare), severe joint pain (rare)
  - GIP-GLP-1 agonists: nausea, vomiting diarrhea, injection site reactions, acute pancreatitis (rare)[18,24]
  - GLP-1 agonists: nausea, vomiting, diarrhea, injection site reactions, acute pancreatitis (rare)
  - Insulins: hypoglycemia, lipohypertrophy, weight gain, local and systemic hypersensitivity reactions (rare)
  - SGLT-2 inhibitors: increased risk of genitourinary infections, reduced intravascular volume resulting in hypotension, hyperkalemia, risk of diabetic ketoacidosis
  - SUs, repaglinide: hypoglycemia, weight gain
  - TZDs: weight gain, fluid retention, hemodilution, worsening heart failure, macular degeneration, increased risk of fractures and possibly bladder cancer
- Safety
  - Sick day management (SADMANS)[33]
  - Hypoglycemia
  - Ketoacidosis

Follow Up[34,35]

- When adjusting medications, follow up within three months.
  - Establish a follow-up plan and set triggers when alternative therapies will be considered (e.g., if A1C increases > x%; signs/symptoms of hyperglycemia).
- Assess medication adherence, injection technique/administration, glycemic control, clinical status changes (including renal health and cardiovascular health), adverse effects, and safety.
- If not at glycemic targets:
  - Consider dose titration if not at maximum recommended dose (cautions: consider risk of hypoglycemia if applicable; maximum doses of SGLT-2 inhibitors provide little additional A1C lowering compared to lower doses).
  - Add another antihyperglycemic agent from a different class, and/or add/intensify insulin regimen.
  - Consider referral to diabetes education clinic for assistance with behavioral modifications and goalsetting.

When Ozempic Returns

- Review therapy with the patient.
  - There may not be a need to return to GLP-1 agonist therapy if treatment goals are achieved and patient is satisfied with regimen.
- Re-initiation of GLP-1 agonist therapy:
  - **Initiate with GLP-1 agonist starting dose** unless fewer than three consecutive doses were missed.
  - DPP-4 inhibitors should not be used in combination with GLP-1 agonists because the combination provides no additional benefit but increases cost.[5] Ensure these agents are discontinued upon restart of GLP-1 agonist therapy.
  - If insulin is continued when GLP-1 agonist therapy is restarted, reduce the dose by 20-30% and adjust.[5]
  - Consider adjustment of SU dose based on A1C[5]:
    - ≤ 7.5%: stop SU
    - 7.6 to 8.5%: reduce dose by 50%
    - > 8.5%: maintain current dose

Abbreviations

A1C=glycated hemoglobin
DPP-4=dipeptidyl peptidase-4
eGFR=estimated glomerular filtration rate
GIP-GLP-1=glucose-dependent insulinotropic polypeptide and glycoprotein-like peptide-1
GLP-1=glycoprotein-like peptide-1
MACE=major adverse cardiovascular events
PO=oral
SGLT-2=sodium-glucose transporter-2
SU=sulfonylurea
subcut=subcutaneous
TZD=thiazolidinedione

27 Nov 2023
Prepared by medSask

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