GLP1-RA (Glucagon-like peptide-1 receptor agonists) "–glutides"

See page 8 for acronym definitions

Monitoring summary:

- ✓ BG
- ✓ Weight
- ✓ GI tolerability
- ✓ Renal function if renal impairment and/or GI side effects
- ✓ Annual eye exam (obtain if possible)
- ✓ Heart rate

Counselling summary:

- ✓ GI tolerability tips and reporting symptoms of pancreatitis, cholecystitis, gastroparesis, and bowel obstruction.
- ✓ What to do if significant GI side effects leading to dehydration (stay hydrated, check BG, meds to hold: SADMANS list[1]).
- ✓ Report vision changes.
- ✓ Consult surgeon +/- diabetes team regarding holding doses before procedures requiring fasting and anesthesia.

Medication names

GLP1-RA medications:

- Dulaglutide (Trulicity®) once weekly injectable
- Liraglutide (Victoza®) once daily injectable
- Lixisenatide (Adlyxine®) once daily injectable
- Semaglutide (Ozempic®) once weekly injectable
- Semaglutide (Rybelsus®) once daily oral

Insulin + GLP1-RA combination medications:

- Insulin glargine + lixisenatide (Soliqua®) once daily injectable
- Insulin degludec + liraglutide (Xultophy®) once daily injectable

GLP1-RA and GIP medication:

- Tirzepatide (Mounjaro®) once weekly injectable

Glucose-lowering mechanisms

- ↑ glucose-dependent insulin release
- ↓ glucagon release
- ↓ appetite
- Delays gastric emptying[2]

Benefits and patient buy-in

- ↓ A1c 0.6-2.0%[3]
- ↓ weight by 1.6-5 kg (benefit for BP, BG and pain)[3]
- Low risk of hypoglycemia[3]
- ↑ insulin sensitivity and ↓ insulin requirements (dose sparing effects)[4]
- Weekly subcutaneous dulaglutide (Trulicity®), weekly subcutaneous semaglutide (Ozempic®), and daily subcutaneous liraglutide (Victoza®) ↓ CV risk in patients with T2DM and history of CVD, CKD or a high CVD risk.[4]
- Possible renal risk reduction (much less evidence than with SGLT2is and is limited to surrogate measures and secondary endpoints).[3]
- Once weekly injection options.
- Patients report less pain with injection compared to finger pokes for BG checks.

Contraindications

- Pregnancy, planning to become pregnant or breastfeeding[2]
- Type I diabetes[2]
- Personal or family history of medullary thyroid cancer[2]
- Personal or family history of multiple endocrine neoplasia syndrome type 2[2]

Warnings and precautions

Reduced appetite and weight loss:

- **Consider alternate treatment** if weight loss and reduced appetite could be detrimental.
- **Monitor** weight and oral intake.
- **Counsel** to report worsening of oral intake and problematic weight loss.

Surgical/procedural complications:

- Aspiration has been reported with surgeries requiring anesthesia.[5,6]
- Incomplete bowel preparation has been reported for colonoscopies.
- **Coordinate** with the surgical team about whether this medication needs to be held before a procedure and when it can be restarted. Re-titration may be needed.
- **Caution** in patients who may be at higher risk of DKA. Interim treatment for BG may be needed. Consult an endocrinologist if needed.

Gastroparesis and ileus:

- **Caution** in patients who have gastroparesis, constipation, or other GI conditions.[2]
- **Monitor** for changes in GI symptoms and frequency of bowel movements.
- Slower titration is a reasonable precaution.
- **Counsel** on eating small, more frequent meals and reporting any worsening symptoms.

Heart rhythm/rate changes:

- May ↑ heart rate and PR interval.[2]
- **Caution** in patients who have a history of arrhythmia such as tachyarrhythmias or patients sensitive to tachycardia.

Cholecystitis:

- **Caution** in patients with a history of cholecystitis/cholelithiasis.[4]
- **Counsel** on how to identify cholecystitis symptoms (upper right stomach pain that worsens with deep breaths and may radiate to the back, +/- vomiting) and to seek immediate medical attention if symptoms arise.

Pancreatitis:

- **Consider alternate treatment** in patients with a history of pancreatitis.[2]
- **Counsel** on how to identify pancreatitis (severe pain in stomach that may radiate to the back, +/- vomiting) and to seek immediate medical attention if symptoms arise.

Acute kidney injury:

- **Caution** in patients who have CKD.[2]
- **Monitor** for diarrhea, vomiting and signs/symptoms of dehydration or AKI.
- **Counsel** on staying hydrated and prepare a "Sick Day Plan" (e.g., SADMANS[1]) if dehydrated.

Retinopathy (3% semaglutide SC vs 1.8% placebo):[4]

- **Caution** and consider ophthalmology consult if patient has diabetic retinopathy.
- **Monitor** to ensure patient has a baseline/annual optometry exam to identify retinopathy (consider obtaining optometrist report).
- Slower titration is a reasonable precaution as risk may be related to rapid ↓ in A1c.[4]
- **Counsel** to report any vision changes.

Adjusting other drugs

- Sulfonylureas (SU): consider SU dose ↓ due to risk of hypoglycemia. **Monitor** for hypoglycemia.[2]
- Insulin: insulin dose was ↓ by 20% in trials due to risk of hypoglycemia. **Monitor** for hypoglycemia.[2]
- Do not use with DPP4i due to redundant mechanisms of action. There are no specific safety concerns but the combination has not been studied.[2]

Common side effects and counselling tips

GI effects (nausea, vomiting, diarrhea, dyspepsia, gastroparesis and ↓ appetite) are common with initiation:

- **Counsel** "No one enjoys the first few weeks". GI effects often resolve with time and may be a signal of efficacy.
- **Monitor** to establish tolerability during initiation and dose changes.

GI disturbances can cause dehydration +/- BG changes:

- **Counsel** to drink fluids to prevent dehydration and when to hold other medications on SADMANS list.[1]
- **Counsel** to check BG and how to manage hypoglycemia.
- **Monitor** for diarrhea, vomiting, BG changes, and signs/symptoms of dehydration or AKI.

To minimize GI side effects:

- Eat smaller, more frequent meals.
- Eat slowly and stop eating when full.
- Avoid fatty and spicy food.
- Start low and titrate dose slowly.
- Consider dosing at bedtime.

Common side effects and counselling tips (continued)

Off-label:

- Weekly injectable formulations can initially be given q8, q9 or q10 days to possibly reduce the risk of GI side effects.
- Slower titration is also a reasonable precaution to possibly ↓ retinopathy risk.
- **Note**: the off-label "10 clicks" method for initiating semaglutide (Ozempic®) is no longer 10 clicks with the new semaglutide (Ozempic®) pens. The manufacturer recommends against counting clicks due to inaccurate dosing and wastage.
- **Note**: the off-label practice of combining with Janumet XR® to maintain ODB-covered long-acting metformin while titrating semaglutide (Ozempic®) is no longer an option as the LU code for semaglutide (Ozempic®) specifies it cannot be combined with a DPP4i.

Rotate injection site:

- Absorption: abdomen = arms = thighs.
- Avoid lipohypertrophic areas (GLP1-RA do not cause lipos; insulin does), scars, hair roots and moles.

SGLT2i (Sodium-glucose cotransporter-2 inhibitors) "–gliflozins" " ("flow" sugar)

See page 8 for acronym definitions

Monitoring summary:

- ✓ SCr, K+, ACR (baseline)
- ✓ SCr, K+ 2-4 weeks after initiation
- ✓ BG
- ✓ Weight
- ✓ BP
- ✓ Foot care
- ✓ Genitourinary infections

Counselling summary:

- ✓ Urinary frequency/volume (take in morning)
- ✓ Genital hygiene and managing infections
- ✓ Foot care and reporting changes
- ✓ Hypotension (check BP, hydrate, arise slowly)
- ✓ When to hold (SADMANS list,[1] 3 days pre-op, acute illness)
- ✓ Euglycemic DKA (symptoms, no keto diet)

Medication names

- Canagliflozin (Invokana®)
- Dapagliflozin (Forxiga®, generics)
- Empagliflozin (Jardiance®)
- Canagliflozin + metformin (Invokamet®)
- Dapagliflozin + metformin (Xigduo®)
- Empagliflozin + metformin (Synjardy®)

Glucose-lowering mechanisms

- ↓ renal tubular glucose reabsorption

Benefits and patient buy-in

- ↓ A1c 0.5-0.7%[3]
- ↓ weight 2-3 kg (benefit for BP, BG and pain)[3]
- Low risk of hypoglycemia[3]
- ↓ CV/MACE risk[3] in patients with T2DM and a history of ASCVD or CKD[4]
- ↓ HHF in patients with T2DM and a history of HFrEF or HFpEF, CKD, or high risk for ASCVD[4,7,8]
- ↓ HHF in patients without T2DM and a history of HFrEF or HFpEF[8]
- ↓ Nephropathy in patients with T2DM and a history of ASCVD, CKD, or high risk for ASCVD[4]
- ↓ Nephropathy in patients with or without diabetes and a history of HFrEF[7,8], eGFR 25-90 mL/min/1.73m^2 or UACR >200 mg/g[8,9]
- ↓ all-cause mortality in patients with T2DM and a history of CKD, HFrEF or ASCVD[8]
- **Note**: Glucose-lowering efficacy may be reduced in CKD (eGFR < 45 ml/min/1.73m^2), but renal and heart failure benefits persist.[10,11]

Contraindications

- People who are pregnant, planning to become pregnant, or breastfeeding
- People who are at a high risk for DKA:
  - Type I diabetes
  - History of DKA
  - People who follow a restrictive carbohydrate (e.g., keto) diet
- CKD:
  - Evidence for renal dosing is evolving and varies based on product and indication.[10-12]
  - Please check the most recent product monograph for the most up-to-date information.
  - Consult nephrology and/or cardiology/internal medicine regarding medication continuation and dosing adjustments in advanced CKD eGFR < 30 mL/min/1.73m^2.

Warnings and precautions

Lower extremity amputation:[13]

- **Caution**: ~2x ↑ risk of surgical lower limb amputation (mostly toe/midfoot) in two canagliflozin trials.
- **Caution** in patients with prior amputation, PAD, neuropathy, and diabetic foot ulcers.
- **Counsel** on proper foot care, monitor feet, maintain hydration, and to seek medical attention if any changes.
- **Monitor** for PAD, neuropathy, ulcers, infections.
- **Discontinue** if complication develops that may precede amputation (i.e., lower-extremity skin ulcer, infection, osteomyelitis, gangrene).

AKI:

- **Caution**: Increased risk in older adults, CKD, use with diuretics, NSAIDs, ARNI/ACEIs/ARBs.[3]
- Consider ↓ dose of diuretic(s) and/or other higher-risk meds if appropriate.
- **Counsel** on staying hydrated and prepare a "Sick Day Plan" (e.g., SADMANS[1]) if dehydrated. Resume when dehydration, low oral intake and acute illness resolves.[8]
- **Monitor**:[3]
  - Baseline: SCr, K+, ACR
  - 2-4 wks: SCr, K+
  - Periodically: SCr, K+, ACR.
- eGFR drops ~5 ml/mL in first 3 months[14,15] but resolves over 18 months.[16]
- **Discontinue** if >30% increase in SCr.

DKA:[11,12]

- **Avoid** in patients with a history of DKA and patients who follow a keto diet.
- **Caution** in patients with low- carb diets or fasting;[4] insulin deficiency (pancreatic disorder or insulin dose reductions); alcohol use; intense exercise; acute illness/hospitalization.[1,7]
- **Counsel** on symptoms of DKA (confusion, slurred speech, sweet/metallic taste, sweet smelling breath, unusual tiredness/fatigue, excessive thirst, ↓ appetite, SOB, tachypnea, tachycardia).
- **Counsel** that DKA may occur with a normal BG and to seek immediate medical attention if symptoms arise.
- **Counsel** to not combine with a keto diet and when to hold (3+ days before major surgery; acute illness).

Other:

- 20 possible cases of pancreatitis.[18]
- Small increased risk of Fournier's gangrene.[3]
- Increased risk of fractures was observed in canagliflozin trials.[3]

Adjusting other drugs

- Consider reducing the dose of sulfonylureas and insulin when starting an SGLT2i due to the risk of hypoglycemia.[11,12] **Monitor** for hypoglycemia.
- Use with caution in patients taking diuretics (especially loop diuretics), due to increased risk of volume depletion.[12] Dose adjustments may be needed. **Monitor** for volume depletion and AKI.

Common side effects and counselling tips

Diuretic effects:

- **Counsel** to take in morning or when diuretic effects are not inconvenient.[3] Diuretic effect usually subsides with time.
- **Counsel** to maintain adequate hydration.
- Consider ↓ dose of diuretic(s).
- **Monitor** urinary symptoms and fluid status.
- **Caution** in benign prostatic hyperplasia and/or patients with existing urinary incontinence/frequency.

Genitourinary infections (especially mycotic):[4]

- **Counsel** on hygiene and symptom awareness (and what to do).
- **Avoid** if history of severe and/or recurrent infection despite appropriate treatment.

Hypotension:[3]

- **Counsel** to arise slowly (orthostatic changes).
- **Monitor** blood pressure, volume status, signs of dehydration.
- May consider ↓ other BP medications (especially diuretics) and medications that increase risk of falls.

Metformin

See page 8 for acronym definitions

Glucose-lowering mechanisms

- ↓ gluconeogenesis
- ↓ glucose absorption
- ↑ insulin sensitivity

Benefits and patient buy-in

- First line therapy: metformin = background therapy in major RCTs of newer agents[3]
- ↓ MACE, microvascular disease, and mortality[19]
- ↓ A1c 1.0%
- ↓ weight 2.9 kg (benefit for BP, BG, pain)[3]
- Excellent safety profile
- Low risk of hypoglycemia[3]
- Cost-effective; many combinations[3]

Contraindications

- Unstable and/or type I diabetes
- Acute or chronic metabolic acidosis
- Unknown or unstable renal function
- History of lactic acidosis

Warnings and precautions

Lactic acidosis:

- **Caution** in patients with hepatic disease and patients who have excessive alcohol intake.
- **Monitor** SCr annually and prn for CKD.[3]
  - eGFR 30-45 mL/min/1.73m^2: max ≤1000 mg/day.
  - eGFR <30 mL/min/1.73m^2: avoid (some specialists consider low dose if eGFR is stable).
- **Counsel** on staying hydrated and prepare a "Sick Day Plan" (e.g., SADMANS[1]) if dehydrated.
- **Counsel** to hold for 48-hour post-contrast/iodinated dye.
- **Monitor** for hepatic dysfunction as indicated.

Vitamin B12 deficiency:

- 10-20% of patients may develop B12 deficiency after 4 years of treatment.[20]
- **Monitor** Hg and B12 level q1-2 years.[3]

Common side effects and counselling tips

To minimize GI side effects:

- Start by taking with the largest meal of the day.[3]
- Titrate every 1-2 weeks to avoid GI side effects (i.e., 250 mg once daily and ↑ as slowly as needed).[3]
- Use highest tolerated dose (85% of effect at 1500 mg/day, mortality benefit at 2550 mg/day).[3]
- ER formulations may have fewer GI side effects, but also more expensive.[3]
  - Metformin/sitagliptin (Janumet XR®) is the only ER formulation covered by ODB.
- Dose daily or bid (not tid or qid).

Sulfonylureas

See page 8 for acronym definitions

Glucose-lowering mechanisms

- ↑ insulin
- Efficacy may ↓ over time as pancreatic function declines.

Benefits and patient buy-in

- ↓ A1c 0.6-1.2%[3]
- Low cost for medication (for some patients, costs of monitoring BG may outweigh this benefit).[3]
- Possible microvascular benefits; commonly used in regimens for glycemic control studies.

Adjusting other drugs[21]

- Sulfonylureas should be dose-reduced by 50% or discontinued when starting a basal insulin.
- Discontinue sulfonylureas when starting a prandial insulin.
- Insulin dose should be reduced when initiating a sulfonylurea.
- **Monitor** for hypoglycemia when sulfonylureas are combined with insulin.

Contraindications[22]

- Pregnancy, planning to become pregnant or breastfeeding
- Unstable and/or type I diabetes (especially juvenile diabetes), DKA, or diabetic coma
- Acute illness, trauma, infection or surgery
- Severe hepatic impairment
- Severe renal impairment
- Treatment with miconazole via systemic route or oromucosal gel

Warnings and precautions

Hypoglycemia:[3]

- **Caution** in older adults and those with renal impairment.
- Risk is relative to intensity of BG lowering regimen.
- Risk may be ↓ with long-acting agents (i.e., gliclazide [Diamicron MR®]).[3]
- Gliclazide (Diamicron MR®) should be dosed once a day in the morning – do not split dose bid.[22]
  - Giving this medication in the evening increases risk of nocturnal hypoglycemia.
- **Counsel** on staying hydrated and prepare a "Sick Day Plan" (e.g., SADMANS[1]) if dehydrated.
- **Counsel** on hypoglycemia management.

Common side effects and counselling tips

- Weight gain: 1.2-3.2 kg[3]

Notes: **ACEIs** = angiotensin-converting enzyme inhibitors, **ACR** = urine albumin to creatinine ratio, **AKI** = acute kidney injury, **ARBs** = angiotensin receptor blockers, **bid** = twice daily, **BG** = blood glucose, **BP** = blood pressure, **CKD** = chronic kidney disease, **CV** = cardiovascular, **DKA** = diabetes ketoacidosis, **DPP4i** = dipeptidyl peptidase-4 inhibitors, **eGFR** = estimated glomerular filtration rate, **ER** = extended release, **GI** = gastrointestinal, **GLP1-RA** = glucagon-like peptide-1 receptor agonists, **IR** = immediate release, **K+** = potassium, **MACE** = major adverse cardiac events, **mg** = milligram, **MR** = modified release, **NIHB** = Non-Insured Health Benefits, **NSAIDs** = nonsteroidal anti-inflammatory drugs, **ODB** = Ontario Drug Benefit, **PAD** = peripheral artery disease, **q** = every, **qid** = four times daily, **RCT** = randomized control trial, **SC** = subcutaneous, **SCr** = serum creatinine, **SGLT2i** = sodium-glucose cotransporter-2 inhibitors, **SMBG** = self-monitoring of blood glucose, **tid** = three times daily, **XR** = extended release

References

1. RxFiles. Type 2 diabetes and sick days: Medications to pause [Internet]. [cited 2020 Dec 22]. Available from: https://www.rxfiles.ca/rxfiles/uploads/documents/SADMANS-Rx.pdf.
2. Novo Nordisk Canada Inc. Product monograph: Ozempic® [Internet]. 2020 [cited 2024 April 23]. Available from: https://pdf.hres.ca/dpd_pm/00074964.PDF.
3. Centre for Effective Practice. Type 2 diabetes: Non-insulin pharmacotherapy [Internet]. 2023. Available from: https://cep.health/clinical-products/type-2-diabetes/.
4. Lipscombe L, Butalia S, Dasgupta K, Eurich DT, MacCallum L, Shah BR, et al. Pharmacologic glycemic management of type 2 diabetes in adults: 2020 update. Can J Diabetes. 2020 Oct 1;44(7):575-591.
5. Gulak MA, Murphy P. Regurgitation under anesthesia in a fasted patient prescribed semaglutide for weight loss: A case report. Can J Anesth. 2023 Aug;70(8):1397-1400.
6. Marroquin-Harris M, Olesnicky B. Aspiration risk with glucagon-like peptite 1 (GLP-1) agonists. Anaesthesia. 2023;78(12):1524.
7. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. Can J Cardiol. 2021 Apr;37(4):531-546.
8. Mancini GBJ, O'Meara E, Zieroth S, Bernier M, Cheng AYY, Cherney DZI, Connelly KA, et al. 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults. Can J Cardiol. 2022 Aug;38(8):1153-1167.
9. Fryml E, Lanktree MW. Sodium-glucose cotransporter-2 inhibitors in patients without diabetes. CMAJ. 2023 May;195(17): E619.
10. Janssen Inc. Product monograph: INVOKANA® [Internet]. 2023 [cited 2023 Jun 28]. Available from: https://pdf.hres.ca/dpd_pm/00069624.PDF.
11. AstraZeneca Canada Inc. Product monograph: FORXIGA® [Internet]. 2023 [cited 2024 May 1]. Available from: https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/forxiga-product-monograph-en.pdf.
12. Boehringer Ingelheim (Canada) Ltd. Product monograph: Jardiance® [Internet]. 2023 [cited 2023 Jun 28]. Available from: https://pdf.hres.ca/dpd_pm/00071040.PDF.
13. Government of Canada HC. INVOKANA® (canagliflozin) and INVOKAMET® (canagliflozin and metformin): Risk of lower limb amputation [Internet]. 2017 [cited 2020 Dec 22]. Available from: https://recalls-rappels.canada.ca/en/alert-recall/invokanar-canagliflozin-and-invokametr-canagliflozin-and-metformin-risk-lower-limb..
14. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015 Nov 26;373(22):2117–28.
15. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017 Aug 17;377(7):644–57.
16. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424.
17. Goldenberg RM, Berard LD, Cheng AYY, Gilbert JD, Verma S, Woo VC, et al. SGLT2 inhibitor–associated diabetic ketoacidosis: Clinical review and recommendations for prevention and diagnosis. Clin Ther. 2016 Dec;38(12):2654-2664.e1.
18. Government of Canada HC. Summary safety review: SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) [Internet]. 2014 [cited 2020 Dec 22]. Available from: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR00204.
19. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998 Sep;352(9131):854–65.

20. Jager J de, Kooy A, Lehert P, Wulffelé MG, Kolk J van der, Bets D, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010 May 20;340:c2181.
21. Centre for Effective Practice. Type 2 diabetes: Insulin therapy [Internet]. 2023 [cited 2024 May 22]. Available from: https://cep.health/diabetes.
22. Servier Canada Inc. Product monograph: Diamicron® MR [Internet]. 2019 [cited 2024 May 22]. Available from: https://pdf.hres.ca/dpd_pm/00053765.PDF.