DALHOUSIE UNIVERSITY
FACULTY OF MEDICINE
Academic Detailing Service

PRESCRIBING CONSIDERATIONS for SGLT-2 Inhibitors and GLP-1 Agonists in T2DM

SGLT-2 Inhibitors

Sick Day Management

- Advise people with T2DM to temporarily stop the following medications during times of acute illness and decreased fluid intake (e.g., vomiting, diarrhea, and fever), to reduce risk of adverse effects and acute kidney injury (AKI):

S	Sulfonylureas
A	ACE inhibitors
D	Diuretics, direct renin inhibitors
M	Metformin
A	Angiotensin receptor blockers
N	Nonsteroidal anti-inflammatories
S	***SGLT-2 inhibitors***

Adapted from Diabetes Canada Guidelines. Can J Diabetes 42 (2018) S316.

- Resume medications at usual dose post illness.

Potential SGLT-2 Inhibitor Drug Interactions

- *Hypoglycemia:* Re-evaluate dose and use of concomitant insulin or sulfonylurea upon initiation of SGLT-2 inhibitor to reduce risk.
- *Hypotension:* Caution when used in combination with antihypertensive drugs, particularly loop diuretics, due to SGLT-2 inhibitor diuretic effects.
  - Note: Canagliflozin is *not recommended* in combination with loop diuretics according to the product monograph.

Risk of Diabetic Ketoacidosis (DKA)

- People taking SGLT-2 inhibitors may develop DKA despite normal blood glucose (BG) levels.
- Risk factors for DKA and strategies to minimize risk:

Risk Factor	Mitigation Strategy
Acute serious illness	• Hold SGLT-2 inhibitor at onset of illness • Restart when feeling well and able to eat and drink
Major surgery	• Hold SGLT-2 inhibitor 3 days before surgery • Restart once physiological stress has resolved, feeling well and able to eat and drink
Bariatric surgery	• Hold SGLT-2 inhibitor during preoperative low-carbohydrate diet*; reassess postoperatively
Low carbohydrate intake*	• Hold SGLT-2 inhibitor • Restart if low carbohydrate diet* is discontinued
Excessive intake of alcohol**	• Stop SGLT-2 inhibitor immediately • Reassess therapy if alcohol intake is reduced**

**Diabetes Canada defines low-carbohydrate intake as 50-130 g/day. This definition is inconsistent in the literature.*
***Not defined in the literature*

Adapted from Clin Ther 2016;38:2654–64.

- A sudden omission or significant reduction of insulin dose may precipitate DKA.

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SGLT-2 Inhibitors (continued)

Considerations in Renal Impairment

- BG lowering effect of SGLT-2 inhibitors is attenuated when eGFR falls below 45 mL/min/1.73 m^2. Evidence evaluating major adverse CV events & HF outcomes below this threshold is very limited, but evidence supports the possibility of continued benefit in kidney outcomes based on subgroup analyses in renal trials (DAPA-CKD[1] & EMPA-KIDNEY[2]).
- Renal considerations for starting or stopping therapy:

Drug	*Initiation* of therapy not recommended if eGFR below	*Renal* Contraindications
Canagliflozin	30 mL/min/1.73 m^2	Dialysis
Dapagliflozin	25 mL/min/1.73 m^2	Dialysis
Empagliflozin	30 mL/min/1.73 m^2	eGFR < 20 mL/min/1.73 m^2 Dialysis

- A decrease in eGFR of ~3 to 5 mL/min was observed in the treatment groups during the first 4-8 weeks of the CV outcome trials, which may be confused with AKI.[3,4]
  - Upon cessation of therapy, the decrease was reversed.
  - Following the initial decline, eGFR stabilized in the SGLT-2 inhibitor groups while it continued to gradually decline in standard care groups for the remainder of the studies.

[1] N Engl J Med 2020;383:1436-46, [2] N Engl J Med 2023;388:117-27, [3] N Engl J Med. 2016 Jul 28;375(4):323–34., [4] Circulation. 2018;138:1537–1550.

GLP-1 Agonists

How to Minimize Gastrointestinal (GI) Adverse Effects

- GI adverse effects (e.g., nausea, vomiting, and diarrhea) are well known adverse effects associated with GLP-1 agonists.
- No high-quality evidence to support strategies intended to improve tolerability exists, but the risk of harm is very low.
- Consider
  - Starting at a low dose and titrating slowly
  - Eating smaller, more frequent meals
  - Choosing low fat foods and eating slowly
  - Stopping oral intake when satiety is experienced
  - Administering dose at bedtime

Potential GLP-1 Agonist Drug Interaction

- *Hypoglycemia*: Re-evaluate dose and use of concomitant insulin or sulfonylurea upon initiation of GLP-1 agonist to reduce risk.

How many doses are in each GLP-1 agonist pre-filled pen?		
Liraglutide: 30 doses x 0.6 mg or 15 doses x 1.2 mg or 10 doses x 1.8 mg		
Semaglutide: 8 doses x 0.25 mg or 4 doses x 0.5 $mg^{1.5mL}$ or 4 doses x 1 mg^{3mL}		
Lixisenatide:	0.05 mg/mL	14 doses x 10 mcg
	0.1 mg/mL	14 doses x 20 mcg
Others: one pen = one weekly dose (e.g. **dulaglutide**)		

Adapted with permission from RxFiles. Available with subscription at www.rxfiles.ca

Drug Tables: SGLT-2 Inhibitors and SGLT-2 Inhibitor Combination Products

SGLT-2 Inhibitors					
Name Generic, *Trade*	**Strength(s)**	**Adult Dose** (Product Monographs)	**Dose Adjustments** (Product Monographs)	**Nova Scotia Pharmacare Status**	**McKesson Cost† (Supply)**
SGLT-2 Inhibitors (MOA: inhibit SGLT-2, reducing reabsorption of glucose from the renal tubular lumen)					
Canagliflozin *Invokana*	100 mg 300 mg	100-300 mg PO daily Take before first meal of day. Swallow whole.	Hepatic • Severe impairment: Use not recommended (not studied) Renal • eGFR 30 to <60 mL/min/1.73 m^2: 100 mg daily • eGFR <30 mL/min/1.73 m^2: Do not *initiate* therapy • eGFR < 30 mL/min/1.73 m^2, albuminuria > 33.9 mg/mmol, and on *established* therapy: May continue at 100 mg daily • CI if on dialysis	Exception status*	$94 (30 days)
Dapagliflozin *Forxiga*	5 mg 10 mg	5-10 mg PO daily HF: 10 mg PO daily CKD: 10 mg PO daily Swallow whole.	Hepatic: • Severe impairment: Use not recommended Renal • eGFR ≥25 mL/min/1.73 m^2: No change in dose • eGFR <25 mL/min/1.73 m^2: Initiation of therapy not recommended • CI if on dialysis	Exception status*	$89 (30 days)
Empagliflozin *Jardiance*	10 mg 25 mg	10-25 mg PO daily HF: 10 mg PO daily Swallow whole.	Hepatic: • Severe impairment: Use not recommended Renal: • Not recommended if eGFR <30 mL/min/1.73 m^2 • CI if eGFR <20 mL/min/1.73 m^2	Exception status*	$90 (30 days)

BG: blood glucose, CI: contraindicated, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, HF: heart failure, MOA: mechanism of action, PO: by mouth, SGLT-2: sodium glucose co-transporter 2
*See Exception Status Criteria at the end of tables.
†Cost for one tablet daily, regardless of strength. Pricing is approximate.
For additional prescribing information, see product monographs.

Last updated: February 2023

Drug Tables: SGLT-2 Inhibitors and SGLT-2 Inhibitor Combination Products

Name Generic, *Trade*	**Strength(s)**	**Adult Dose** (Product Monographs)	**Dose Adjustments** (Product Monographs & Lexi-comp)	**Nova Scotia Pharmacare Status**	**McKesson Cost (Supply)**
Combined Formulations: SGLT-2 Inhibitors + Biguanides					
Empagliflozin + Metformin *Synjardy*	5/500 mg 5/850 mg 5/1000 mg 12.5/500 mg 12.5/850 mg 12.5/1000 mg	1 tablet PO BID with meals In patients already taking metformin, start empagliflozin at 5 mg BID and continue metformin at a similar total daily dose **MAX:** Total daily dose 25/2000 mg	<u>Hepatic:</u> • CI in patients with clinical or laboratory evidence of hepatic disease. <u>Renal:</u> PM: CI in people with renal impairment, e.g. CrCL < 60 mL/min (due to metformin component) Lexi-comp: • eGFR ≥ 45 mL/min/1.73 m^2 – no adjustment; monitor renal function • eGFR 30 to 45 mL/min/1.73 m^2 – US manufacturer does not recommend initiating therapy • eGFR < 30 mL/min/1.73 m^2 – CI • ESRD/ dialysis - CI	Exception status*	$93† (30 days)
Dapagliflozin + Metformin *Xigduo*	5/850 mg 5/1000 mg	1 tablet PO BID with meals **MAX:** Total daily dose 10/2000 mg	<u>Hepatic:</u> • CI in patients with clinical or laboratory evidence of hepatic disease. <u>Renal:</u> PM: CI in people with renal impairment, e.g. CrCL < 60 mL/min Lexi-comp: • eGFR ≥ 45 mL/min/1.73 m^2 – no change • eGFR 30 to < 45 mL/min/1.73 m^2 – initiation of therapy not recommended • eGFR < 30 mL/min/1.73 m^2/dialysis – CI	Exception status*	$80† (30 days)

BID: twice daily, CI: contraindicated, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, PM: product monograph, PO: by mouth, SGLT-2: sodium glucose co-transporter 2
*See Exception Status Criteria at the end of tables.
†Cost for one tablet twice daily, regardless of strength. Pricing is approximate.
For additional prescribing information, see product monographs.

Last updated: February 2023

Drug Tables: SGLT-2 Inhibitors and SGLT-2 Inhibitor Combination Products

Name Generic, *Trade*	**Strength(s)**	**Adult Dose** (Product Monographs)	**Dose Adjustments** (Product Monographs & Lexi-comp)	**Nova Scotia Pharmacare Status**	**McKesson Cost (Supply)**
Combined Formulations Continued: SGLT-2 Inhibitors + Biguanides					
Canagliflozin + Metformin *Invokamet*	50/500 mg 50/1000 mg 150/500 mg 150/1000 mg	1 tablet PO BID with meals In patients already taking metformin, start canagliflozin at 50 mg BID and continue metformin at a similar total daily dose **MAX:** Total daily dose 300/2000 mg Note: XR formulation approved by Health Canada but not yet available.	Hepatic: • CI in patients with clinical or laboratory evidence of hepatic disease. Renal: PM: • CI in people with renal impairment, e.g. CrCL < 60 mL/min • No dose adjustment required provided eGFR > 60 mL/min/1.73 m^2 Lexi-comp: • eGFR ≥ 60 mL/min/1.73 m^2 – no change • eGFR 45 to < 60 mL/min/1.73 m^2 – Max dose canagliflozin 100 mg/day; no dose adjustment for metformin required • eGFR 30 to <45 mL/min/1.73 m^2 – Initiation of therapy not recommended; continuation of existing therapy permitted at canagliflozin dose of 100 mg/day max and metformin dose 500 mg BID max; monitor renal function closely • eGFR < 30 mL/min/1.73 m^2 or dialysis – CI	Not a benefit	$108† (30 days)

BID: two times daily, CI: contraindicated, eGFR: estimated glomerular filtration rate, PM: Product monograph, PO: by mouth, SGLT-2: sodium glucose co-transporter 2, XR: extended release.
†Cost for one tablet twice daily, regardless of strength. Pricing is approximate.
For additional prescribing information, see product monographs.

Last updated February 2023.

Drug Tables: GLP-1 Agonists and GLP-1 Agonist Combination Products

GLP-1 Agonists					
Name Generic, *Trade*	**Strength(s)**	**Adult Dose** (Product Monographs)	**Dose Adjustments** (Product Monographs)	**Nova Scotia Pharmacare Status**	**McKesson Cost† (Supply)**
GLP-1 Receptor Agonists (MOA: mimic actions of GLP-1, thereby ↑ insulin secretion, ↓ glucagon secretion, slow gastric emptying, and ↑ satiety)					
Liraglutide *Victoza*	Prefilled pen: 6 mg/mL	0.6 mg SC daily x 7 days, then 1.2 mg SC daily. May ↑ to 1.8 mg SC daily after 7 days prn. MAX: 1.8 mg SC daily	Hepatic: • No dose adjustment Renal: • Use in ESRD not recommended • Otherwise, no dose change required for ↓ CrCl	Not a benefit	$210-$316 (30 days @ 1.2-1.8 mg/day)
Dulaglutide *Trulicity*	PFS or pens: 0.75 mg/0.5 mL 1.5 mg/0.5 mL	Initiate at 0.75 mg SC once weekly. May ↑ to 1.5 mg SC once weekly. MAX: 1.5 mg SC once weekly	Hepatic: • No dose adjustment Renal: • No dose adjustment	Not a benefit	$230 (28 days @ 0.75-1.5 mg/week)
Lixisenatide *Adlyxine*	Prefilled pens (3 mL): 10 mcg/dose (0.05 mg/mL) 20 mcg/dose (0.1 mg/mL)	10 mcg SC daily x 14 days, then 20 mcg SC daily starting day 15 Administer 60 minutes before any meal of the day	Hepatic: • No dose adjustment Renal: • ESRD, dialysis, severe renal impairment: not recommended	Exception status*	$124 (28 days @ 20 mcg/d)
Semaglutide *Ozempic*	Prefilled pens: 2 mg/pen (1.34 mg/mL) 4 mg/pen (1.34 mg/mL)	0.25 mg SC weekly x 4 weeks, then 0.5 mg SC weekly. May ↑ to 1 mg SC weekly after another 4 weeks. MAX: 2 mg SC weekly	Hepatic: • Use with caution (not studied) Renal: • No dose adjustment • Not recommended in ESRD	Exception status*	$221 (28 days @ 0.5-1 mg/ week)
	Note: 8 mg/pen (2.68 mg/mL) approved by Health Canada but not yet available.				

BID: two times daily, CI: contraindicated, CrCL: creatinine clearance, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, GLP-1: glucagon-like peptide-1, MOA: mechanism of action, PFS: pre-filled syringe, PM: Product monograph, PRN: as needed, SC: subcutaneous.
*See Exception Status Criteria at the end of tables.
†Pricing is approximate.
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Updated February 2023.

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Drug Tables: GLP-1 Agonists and GLP-1 Agonist Combination Products

Name Generic, *Trade*	**Strength(s)**	**Adult Dose** (Product Monographs)	**Dose Adjustments** (Product Monographs)	**Nova Scotia Pharmacare Status**	**McKesson Cost† (Supply)**
GLP-1 Receptor Agonists – Continued					
Semaglutide *Rybelsus*	3 mg 7 mg 14 mg	3 mg PO daily x 30 days, then 7 mg PO daily x 30 days, then May ↑ to 14 mg PO daily prn. Take 30 minutes before first food, beverage, or other PO drugs of the day. Take with ≤ 120 mL water. Swallow whole.	Hepatic: • No dose adjustment Renal: • No dose adjustment	Not a benefit	$227 (30 days @ 7-14 mg/day)
Combination Formulations: Long acting BASAL insulin + GLP-1 Agonist					
Insulin degludec/ liraglutide *Xultophy*	Prefilled pen: 100 units/mL + 3.6 mg/mL	10 units/0.36 mg SC daily start for GLP-1 or basal insulin naïve patients Already on basal insulin/GLP-1: discontinue single agents and start 16 units/ 0.58 mg SC daily Titrate by 2 units once or twice weekly prn MAX: 50 units/1.8 mg daily	Hepatic: • No dose adjustment Renal: • No dose adjustments for mild to moderate impairment (CrCl 30-90 mL/minute) • Severe renal impairment or ESRD: use is not recommended	Not a benefit	$ 107- 335 (30 days @ 16 to 50 units/0.58 to 1.8 mg daily)
Insulin glargline/ lixisenatide *Soliqua*	Prefilled pen: 100 units/mL + 33 mcg/mL	<30 units insulin/day: 15 units/ 5 mcg SC daily start 30–60 units insulin/day: 30 units/10 mcg SC daily start Titrate by 2–4 units weekly prn MAX: 60 units/20 mcg SC daily	Hepatic: • No dose adjustment Renal: • No dose adjustments for mild to moderate impairment (CrCl 30-90 mL/minute) • Severe renal impairment or ESRD: use is not recommended	Not a benefit	$63-250 (30 days @ 15 to 60 units/ 5 to 20 mcg daily)

CrCL: creatinine clearance, ESRD: end-stage renal disease, GLP-1: glucagon-like peptide-1, PO: by mouth, PRN: as needed, SC: subcutaneous
†Pricing is approximate.
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Nova Scotia Pharmacare
EXCEPTION STATUS CRITERIA

June 2022

Canagliflozin (Invokana):

- For the treatment of type 2 diabetes (T2DM) for patients with:
  - Inadequate glycemic control on metformin and a sulfonylurea (SU); and
  - For whom insulin is not an option.

Note:

- 200 mg is not a recognized dose; as such a dose of two 100 mg tablets will not be funded.

Dapagliflozin (Forxiga):

- For the treatment of T2DM when:
  - Added on to metformin for patients:
    - who have inadequate glycemic control on metformin; and
    - who have a contraindication or intolerance to a SU; and
    - for whom insulin is not an option.
- Added on to a SU for patients:
  - Who have inadequate glycemic control on a SU; and
    - who have a contraindication or intolerance to metformin; and
    - for whom insulin is not an option.

Dapagliflozin + metformin (Xigduo):

- For the treatment of T2DM for patients:
  - who are already stabilized on therapy with dapagliflozin and metformin to replace the individual components of dapagliflozin and metformin; and
  - for whom insulin is not an option

Claim Note:

- Must have met criteria for dapagliflozin.

Empagliflozin (Jardiance):

- For treatment of T2DM for patients with:
  - inadequate glycemic control on metformin and a SU; and
  - for whom insulin is not an option

OR

- As an adjunct to diet, exercise, and standard care therapy to reduce the incidence of cardiovascular (CV) death in patients with T2DM and established CV disease (details must be provided as per clinical note below) who have:
  - inadequate glycemic control despite an adequate trial of metformin

Clinical Notes:

- Established CV disease is defined as one of the following (details must be provided):
  - History of myocardial infarction (MI)
  - Multi-vessel coronary artery disease in two or more major coronary arteries (irrespective of revascularization status)
  - Single-vessel coronary artery disease with significant stenosis and either a positive non-invasive stress test or discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection.
  - Last episode of unstable angina >2 months prior with confirmed evidence of coronary multi-vessel or single-vessel disease.
  - History of ischemic or hemorrhagic stroke.
  - Occlusive peripheral artery disease.

Empagliflozin + metformin (Synjardy):

- For the treatment of T2DM in patients who are already stabilized on therapy with empagliflozin and metformin, to replace the individual components of empagliflozin and metformin. Patients must meet coverage criteria for empagliflozin.

Lixisenatide (Adlyxine):

- For treatment of T2DM when added to:
  - Basal insulin for patients who have inadequate glycemic control on basal insulin; or
  - Basal insulin and metformin for patients who have inadequate glycemic control on metformin and basal insulin

Semaglutide (Ozempic):

- For the treatment of T2DM in combination with metformin and a SU, when diet and exercise plus dual therapy with metformin and a SU do not achieve adequate glycemic control.

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