DIABETES PHARMACISTS NETWORK

GLP-1 Receptor Agonists Practice Tool

Indications and Clinical Use

In people with type 2 diabetes to improve glycemic control as:

1. Monotherapy where metformin is inappropriate due to contraindications or intolerance

2. Add-on therapy to one or more antihyperglycemic agents (metformin, sulfonylureas, SGLT2 inhibitors)

Combination with DPP-4 inhibitors is not recommended due to similar mechanism of action.

3. Add-on therapy to basal insulin

Consider add-on therapy before initiating bolus insulin or intensifying insulin because of weight loss and a lower hypoglycemia risk compared to single or multiple bolus insulin injections.

4. Add-on therapy to basal-bolus insulin

5. Certain GLP-1 receptor agonists are recommended in people with type 2 diabetes and cardiovascular disease to reduce the risk of major adverse cardiovascular events. *(See Cardiovascular Outcomes Trials)*

GLP-1 receptor agonists stimulate glucose-dependent insulin release, inhibit glucagon release, slow gastric emptying and increase satiety.

↓ A1C 0.8 - 1.6 % ↓ Body weight 1.6 - 3 kg Low risk of hypoglycemia ↑ Satiety ↓ Blood Pressure ~ 2 mmHg ↑ Heart Rate ~ 2 bpm

Cardiovascular Outcomes Trials

Medication (Trial Name)	Dulaglutide (REWIND)	Exenatide ER (EXSCEL)	Liraglutide (LEADER)	Lixisenatide (ELIXA)	Semaglutide SC (SUSTAIN-6)	Semaglutide PO (PIONEER-6)
Population	66 % had major CV risk factors	73 % had CVD	81 % had CVD, CKD	Recent ACS	83 % had CVD, CKD	85 % had CVD or CKD*
MACE	↓ NNT = 71	↔	↓ NNT = 53	↔	↓† NNT = 43	↔
CV Death	↔	↔	↓ NNT = 77	↔	↔	↓‡
Non-fatal MI	↔	↔	↔	↔	↔	↔
Non-fatal stroke	↓ NNT = 125	↔	↔	↔	↓ NNT = 91	↔

Note: data in table are from separate clinical trials and should not be interpreted as head-to-head comparisons

↓ Superiority ↔ Non-inferiority † Superiority was not pre-specified ‡ Not regarded as significant because of hierarchical statistical testing plan

ACS = Acute Coronary Syndrome; CKD = Chronic Kidney Disease (stage 3 or higher, eGFR < 60 ml/min/1.73m^2); CKD = Chronic Kidney Disease (eGFR = 30-59 ml/min/1.73m^2); CVD = Cardiovascular Disease (coronary artery disease, cerebrovascular disease, peripheral vascular disease); MACE = Major Adverse Cardiovascular Event (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); NNT = Number Needed to Treat*

GLP-1 Receptor Agonists Head-to-Head Trials

🔒 *= Difference in mean weight reduction from baseline* *A1C = difference in mean change in A1C from baseline*

Medication	Semaglutide 14 mg po daily	Semaglutide 1 mg sc wkly	Semaglutide 0.5 mg sc wkly	Lixisenatide 20 mcg sc daily	Liraglutide 1.8 mg sc daily	Exenatide 5 mcg sc bid
Dulaglutide 0.75 mg sc wkly	--	--	A1C: SEMA > DULA 🔒: SEMA > DULA	--	--	A1C: DULA > EXE 🔒: EXE > DULA
Dulaglutide 1.5 mg sc wkly	--	A1C: SEMA > DULA 🔒: SEMA > DULA	--	--	A1C: ↔ 🔒: LIRA > DULA	A1C: DULA > EXE 🔒: ↔
Exenatide 5 mcg sc bid	--	--	--	A1C: ↔ 🔒: ↔	A1C: LIRA > EXE 🔒: ↔	--
Exenatide ER 2 mg sc wkly	--	A1C: SEMA > EXE ER 🔒: SEMA > EXE ER	--	--	A1C: LIRA > EXE ER 🔒: LIRA > EXE ER	A1C: EXE ER > EXE 🔒: ↔
Liraglutide 1.2 mg sc daily	--	A1C: SEMA > LIRA 🔒: SEMA > LIRA	--	--	--	--
Liraglutide 1.8 mg sc daily	A1C: SEMA > LIRA 🔒: SEMA > LIRA	--	--	A1C: LIRA > LIXI 🔒: ↔	--	--

↔ Non-inferiority > Superiority -- Head-to-Head combination has not been studied

ADVERSE EFFECTS AND MANAGEMENT

Gastrointestinal Adverse Effects

• Nausea, vomiting, diarrhea are dose dependent, transient and occur most commonly when initiating or titrating therapy.

• Start at lower doses and titrate –see dosing guidelines.

• Not recommended in patients with gastroparesis or severe gastrointestinal disease.

Advise patients:

• Stop eating when full. Reduce food and fat intake, do not eat while distracted e.g. in front of TV, and avoid trigger foods to lessen nausea and vomiting.

• Stay hydrated. Dehydration from vomiting and diarrhea could cause deterioration in renal function in those with renal impairment.

• Abdominal pain that radiates to the back with or without nausea is an **alarm symptom** (See Pancreatitis).

Injection Site Reactions

• Bruising, pain, irritation, itching or rash may occur at site of injection. Reactions are mild, transient and do not result in therapy discontinuation.

• Injection site nodules can occur with the Exenatide ER formulation. Most are asymptomatic and resolve in 4 to 8 weeks.

Advise patients to:

• Rotate injection site (abdomen, thighs, arms). GLP-1 receptor agonists are absorbed equally from all sites.

• Avoid injecting into lipohypertrophic areas, hair roots, scars, moles and other skin abnormalities.

Diabetic Retinopathy

In the semaglutide cardiovascular outcomes trial (SUSTAIN-6), diabetic retinopathy complications were higher in the semaglutide arm vs placebo (3 % vs 1.8% HR 1.76; 95 % CI 1.11–2.78; p = 0.02) NNH=83. Risk was greatest in those with pre-existing retinopathy. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. However, long-term glucose control may decrease the risk of diabetic retinopathy. Ensure patients are routinely screened for retinopathy and blood glucose and blood pressure are optimized.

NNH = Number Needed to Harm

Pancreatitis

• Consider alternatives for those with a history of pancreatitis or other risk factors for pancreatitis (e.g. gallstones, alcoholism or hypertriglyceridemia).

• Advise patient to watch for signs and symptoms of pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting), after initiation and dose increases.

• If pancreatitis is suspected, discontinue GLP-1 receptor agonist. If pancreatitis is confirmed, do not restart.

Thyroid Cancer

Contraindicated in those with personal or family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2).

GLP-1 agonists have caused treatment-dependant thyroid C-cell tumours in rats but the risk in humans is unknown.

Increased Heart Rate

Caution in those with a condition that may be worsened by this (e.g. tachyarrhythmias).

PR Interval Prolongation

• Prolongation of the PR interval on electrocardiogram may occur.

• Caution in those with underlying structural heart disease, pre-existing conduction system abnormalities (e.g. marked first-degree AV block or second- or third-degree AV block), ischemic heart disease, cardiomyopathies or a history of rhythm disturbances (e.g. tachyarrhythmias).

DOSING AND CONSIDERATIONS

Medication	Starting		If Additional Glycemic Control Needed	Missed Doses
	Initial	Titration		
Dulaglutide (Trulicity®)	0.75 mg sc weekly		Increase to 1.5 mg sc weekly	< 3 days of next dose: skip dose, resume regularly scheduled dose ≥ 3 days of next dose: give dose as soon as possible
Exenatide (Byetta®)	5 mcg sc BID		Increase to 10 mcg sc BID after 1 month	Skip missed dose and give next dose on schedule
	Administer within 60 minutes before two main meals of the day, at least 6 hours apart. Should NOT be administered after a meal.			
Exenatide ER (Bydureon®)	2 mg sc weekly			< 3 days after missed dose: give dose as soon as possible and resume regularly scheduled dose ≥ 3 days after missed dose: skip the dose and wait to take at next scheduled dose
Liraglutide (Victoza®)	0.6 mg sc daily	1.2 mg sc daily after 1 week	Increase to 1.8 mg sc daily after 1 week	Skip missed dose and take on next day
Lixisenatide (Adlyxine®)	10 mcg sc daily	20 mcg sc daily after 2 weeks		Take within the hour prior to the next meal.
	Administer within 60 minutes before any meal of the day			
Semaglutide sc (Ozempic®)	0.25 mg sc weekly	0.5 mg sc weekly after 4 weeks	Increase to 1 mg sc weekly after 4 weeks	≤ 5 days since missed dose: administer as soon as possible and take next dose as usual > 5 days since missed dose: skip dose, administer next dose on schedule
Semaglutide oral (Rybelsus®)*	3 mg po daily	7 mg po daily after 30 days	Increase to 14 mg po daily after 30 days on the 7 mg dose	Skip the missed dose and take on next day
	Administer at least 30 min before the first food, beverage or other oral medications of the day with no more than 4 oz of plain water only. Waiting < 30 min may decrease the effect and waiting > 30 min to eat may increase the absorption.			
Combination Products				
Insulin degludec/ liraglutide (Xultophy®)	16 units sc daily		Titrate up or down by 2 units every 3 to 4 days Maximum dose is 50 units	Resume with the next scheduled dose. > 3 days since last dose: reinitiate at the starting dose (i.e. 16 units) to mitigate any gastrointestinal symptoms
Insulin glargine/ lixisenatide (Soliqua®)	15 units sc daily if previous basal insulin dose < 30 units 30 units sc daily if previous basal insulin dose 30 to 60 units		Titrate up or down by 2 to 4 units every week Maximum dose is 60 units	Dose should be injected within the hour prior to the next meal.
	Administer within 60 minutes prior to the first meal			

- When administering concurrently with insulin or insulin secretagogues (such as sulfonylurea), consider dose reduction of insulin and sulfonylurea to reduce the risk of hypoglycemia.
- Liraglutide, lixisenatide and semaglutide initial doses are sub-therapeutic. Dose titration is intended to decrease GI symptoms.
- Liraglutide is also available as Saxenda® for chronic weight management at a dose of 3 mg sc daily
- Switching from exenatide to exenatide ER may cause transient elevations in blood glucose, which usually improves within first two weeks of therapy
- Do not mix with insulin. Administer as two separate injections at two different injection sites.
- Time of day of administration does not matter unless indicated
- Do not take an extra dose or increase the dose if a dose is missed

Dosing in Chronic Kidney Disease

Medication	CKD 3A (eGFR 45-59 ml/min)	CKD 3B (eGFR 30-44 ml/min)	CKD 4 (eGFR 15-29 ml/min)	CKD 5 (eGFR <15 ml/min)
Dulaglutide	Dose adjustment not required			Caution as safety not established
Exenatide/ Exenatide ER	Dose adjustment not required >50 ml/min	Caution (30-50 ml/min)	Use alternative due to risk of accumulation	
Liraglutide Liraglutide/insulin degludec	Dose adjustment not required			Use alternative as safety not established
Lixisenatide Lixisenatide/insulin glargine	Dose adjustment not required		Use alternative as safety not established	
Semaglutide	Dose adjustment not required		Caution as safety not established	Use alternative as safety not established

For a complete list of references, please go to: https://www.diabetespharmacistsnetwork.ca/glp-1-receptor-agonists-reference-list/

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For more tools, resources and interactice learning modules, visit: https://www.diabetespharmacistsnetwork.ca/

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