Christchurch Medicines Information Service
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medicines.information@cdhb.health.nz 03 364 0900 medicinesinformation.co.nz

SGLT2 Inhibitors and GLP-1 Receptor Agonists

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) e.g. empagliflozin and glucagon-like peptide-1 receptor agonists (GLP1RA) e.g. dulaglutide and liraglutide are increasingly being used in NZ for type 2 diabetes and other conditions such as heart failure and obesity. Currently their funded use is limited to type 2 diabetes under special authority criteria.

Mechanisms of action

- SGLT2i inhibit glucose reabsorption in the renal proximal tubules and increase urinary glucose excretion.
- GLP1RA increase glucose-dependent insulin secretion, reduce glucagon secretion and slow gastric emptying. They also reduce appetite and increase satiety.

Place in therapy

- Lifestyle management and metformin remain first-line treatment for type 2 diabetes.
- SGLT2i and GLP1RA are now the preferred second-line treatments, as their benefit in reducing cardiovascular risk is greater than other diabetes medicines. Regardless of glycaemic control, all patients with type 2 diabetes with a life expectancy more than a year will benefit from metformin and SGLT2i or GLP1RA.
- SGLT2i improve outcomes for patients with heart failure or chronic kidney disease (even in those without diabetes), and are therefore recommended for patients with these co-morbidities.
- GLP1RA likely lead to greater weight loss than SGLT2i, and are recommended if obesity predominates.
- Both classes can be used together, but the current funding restrictions mean only one will be subsidised.
- Empagliflozin is also approved in for heart failure, but is not funded for patients without diabetes.
- Patients who are not eligible for funding, or who will benefit from use of both classes, can choose to self-fund.
- Dipeptidyl peptidase-4 inhibitors (e.g. vildagliptin) increase endogenous GLP1 and are fully funded. Although less effective than GLP1RA, they can be combined with metformin and SGLT2i in most cases.
- Liraglutide is approved but not funded for weight management in obesity. Dulaglutide is not approved or funded for weight loss but is sometimes used.

Practice Points

- SGLT2i and GLP1RA do not themselves cause hypoglycaemia. Significant hypoglycaemia only occurs in patients taking insulin and/or sulfonylureas.
- GLP1RA have a slightly greater glucose-lowering effect than the other non-insulin treatments.

Empagliflozin

Dose	• 10 mg/day orally • increase to 25 mg/day if necessary
Renal impairment	• efficacy decreases with worsening renal function • avoid if eGFR <20 mL/min/1.73m^2
Other medicines	• concomitant insulin or sulfonylureas may need to be reduced
Adverse effects	• polyuria, genitourinary infections • diabetic ketoacidosis: ○ rare but can occur at normal or slightly raised blood glucose. ○ interpret blood glucose with caution as patients can be severely insulin-deficient without high glucose. ○ acute illness, procedures or excess alcohol increase risk. ○ treat with IV glucose, insulin infusion and potassium. • Fournier's gangrene: ○ rare but has high mortality. ○ perineal care and early recognition and treatment reduce risk.

Dulaglutide

Dose	• 1.5 mg/week subcutaneously • higher doses sometimes used but additional effect is modest
Renal impairment	• avoid if eGFR <15 mL/min/1.73m^2
Other medicines	• stop vildagliptin • concomitant insulin or sulfonylureas may need to be reduced
Adverse effects	• gastrointestinal symptoms (common but usually transient) • pancreatitis, bowel obstruction (rare)

Sick-day and peri-procedural management

- Acute illness: withhold SGLT2i and check blood ketones.
- Minor day-stay procedures including bowel prep: stop SGLT2i the day before and day of surgery.
- All other procedures: stop SGLT2i 2 days before and the day of surgery.
- Restart SGLT2i when eating and drinking normally.
- GLP1RA can be continued.

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