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Empagliflozin and dulaglutide in type 2 diabetes

NZ is funding two medicines in new classes for the treatment of type 2 diabetes.[1] These will be second line options after metformin, and favoured for patients at high risk of cardiovascular or renal complications. They are subject to special authority criteria.[1-3] Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, is funded from 1 February 2021. Dulaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is awaiting registration with Medsafe.

Mechanisms of action

SGLT2 inhibitors (empagliflozin) increase urinary glucose excretion by inhibiting glucose uptake transporters in the renal proximal tubules.[4]

GLP-1 analogues (dulaglutide) are synthetic versions of a peptide hormone released by the gut into the portal circulation in response to food.[5] They increase insulin and reduce glucagon secretion and slow gastric emptying.[5,6]

Place in therapy

Empagliflozin and dulaglutide are additional second line treatment options for the treatment of type 2 diabetes.[7] Lifestyle changes and metformin remain first line treatment.

Patients who may particularly benefit from use

Both empagliflozin and dulaglutide reduce adverse outcomes associated with diabetes.[8-11] SGLT2 inhibitors improve heart failure and reduce progression of diabetic kidney disease with albuminuria.[2,3,11] GLP-1 analogues decrease weight more than other medicines for diabetes. Both have been shown to improve cardiovascular outcomes.

Neither cause hypoglycaemia, however, care should be taken if used concurrently with sulfonylureas or insulin. While their effect on blood pressure is modest, they can increase postural hypotension.

Precautions

SGLT2 inhibitor use increases risk of diabetic ketotacidosis, especially in patients who have insulin reduced or withheld.

Sick day management[12]

If a patient is acutely unwell withhold SGLT2 inhibitors and restart when the patient is eating and drinking. GLP-1 receptor agonists can be temporarily withheld if the unwell patient experiences nausea, vomiting and anorexia, as they can exacerbate these symptoms.

Peri-procedural management (including bowel prep)[13]

Consider stopping SGLT2 inhibitors just prior to starting bowel prep and before surgical procedures to minimise the risk of DKA (see HealthPathways)[17-19]. GLP-1 receptor agonists should be stopped on the day of the procedure.

Table 1: Empagliflozin[4,14]

Presentation[1]	10mg tablet 25mg tablet 5mg or 12.5mg tablet + metformin 500mg 5mg or 12.5mg tablet + metformin 1000mg
Dosing	10mg once daily, increased to 25mg once daily if necessary
Half-life, t1/2	~12 hours
Elimination	Glucuronidated
Renal impairment	Not registered or funded if eGFR<30mL/min/1.73m^2

Table 2: Dulaglutide[15]

Presentation[1]	1.5mg/0.5mL pre-filled pen
Dosing	Weekly, and the amount can be uptitrated
Half-life, t1/2	~5 days
Elimination	Protein catabolism
Renal impairment	Seek specialist advice if eGFR <15mL/min/1.73m^2

Adverse effects[16]

Empagliflozin has an increased risk of diabetic ketoacidosis (DKA) (~1/1000 years). It increases the risk of genitourinary infections, these are generally mild but rare cases of necrotising fasciitis are reported.

Dulaglutide frequently causes gastrointestinal symptoms such as nausea and anorexia, this is usually transient and improves with continued treatment. Occasionally the GI effects are severe and preclude use.

SGLT2 inhibitors and euglycaemic diabetic ketoacidosis [14]

- SGLT2 inhibitor increases risk of DKA in patients with type 2 diabetes.
- In eDKA glucose levels are typically 10-20 mmol/L, because of the effect of the SGLT2 inhibitor.
- When first prescribed, caution is needed particularly if reducing insulin or ceasing sulphonylureas. Patients should be informed of the symptoms of DKA.
- Patients with symptoms should be tested for raised blood ketones, even if blood glucose levels are near normal (urine ketone testing may be unreliable)
- If ketoacidosis is suspected, empagliflozin should be discontinued and immediate medical attention sought for treatment with insulin.

For further information

- NZ guidelines https://t2dm.nzssd.org.nz/Subject-21-Non-insulin-medications
- Consider consulting the diabetes service for complex patients

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