Empagliflozin (Jardiance) is the third SGLT2 inhibitor available for the treatment of type 2 diabetes. Here we present the clinical data relating to its efficacy and adverse events.

**KEY POINTS**
- Empagliflozin (Jardiance) is the third SGLT2 inhibitor for type 2 diabetes
- It is licensed as monotherapy when metformin is inappropriate and as add-on therapy to other glucose-lowering agents, including insulin
- The recommended dose is 10 or 25 mg once daily
- In clinical trials over 24–52 weeks, empagliflozin reduced mean HbA1c by 0.4–0.9 per cent compared with placebo
- Patients treated with empagliflozin lost about 2 kg over 24 weeks, and 3–4 kg in those using insulin
- Genital infections were reported by about 4 per cent of patients
- The incidence of hypoglycaemic events is increased when empagliflozin is added to a sulfonylurea or insulin
- A month’s treatment with empagliflozin costs £36.59

### Empagliflozin

Empagliflozin is licensed as monotherapy when metformin is inappropriate and in combination with other glucose-lowering drugs, including insulin, for the treatment of adults with type 2 diabetes. The recommended dose is initially 10 mg once daily, increasing if necessary to 25 mg once daily in patients with adequate renal function (eGFR ≥60 ml/min/1.73 m²). The dose of insulin or a sulfonylurea may need to be lowered to reduce the risk of hypoglycaemia after adding empagliflozin. No clinically significant drug interactions are known.

Treatment with empagliflozin should not be initiated in patients with inadequate renal function (eGFR < 60 ml/min/1.73 m²). Renal function should be measured before and at least annually during treatment. The dose should be reduced to 10 mg/day if renal function falls below 60 ml/min/1.73 m² during treatment, and discontinued if it is persistently below 45 ml/min/1.73 m².

No dose adjustment is recommended for people with hepatic impairment, though empagliflozin is not recommended when hepatic function is severely impaired. There is also no dose adjustment for age; patients aged ≥ 75 are at increased risk of volume depletion and, due to lack of experience, empagliflozin is not recommended for patients aged ≥ 85.

### Clinical trials

Empagliflozin has been evaluated in 24-week placebo-controlled trials as monotherapy in previously untreated patients (with sitagliptin as an active control) and as add-on therapy with metformin, metformin plus a sulfonylurea, pioglitazone and basal insulin. The primary end-point in each was change in HbA1c. Patients tended to be middle-aged (mean about 55 years) with a baseline HbA1c about 8.0 per cent and a BMI of about 32 kg/m² (32 kg/m² in the insulin trial).

As monotherapy, empagliflozin significantly reduced HbA1c compared with placebo (by 0.74 per cent at 10 mg/day and 0.85 per cent at 25 mg/day); this was similar to the improvement in glycaemic control in patients treated with sitagliptin 100 mg/day. Patients treated with empagliflozin lost approximately 2 kg and blood pressure was slightly reduced compared with placebo over 24 weeks.

As add-on therapy to metformin alone or with a sulfonylurea, or in addition to pioglitazone with (mostly) or without metformin, empagliflozin significantly reduced...
HbA1c (by about 0.6 per cent) and BMI (by 1.6–2kg) compared with placebo, with the higher dose slightly more effective.

Non-blinded extension studies up to 52 weeks showed these gains were sustained and that empagliflozin was non-inferior to glimepiride for glycaemic control, with a reduction rather than a gain in mean body weight (–3.2kg vs.+1.6kg). Overall, empagliflozin reduced HbA1c more in patients with worse glycaemic control at baseline (0.40 per cent at 10mg/day and 0.46 per cent at 25mg/day for HbA1c <8.0 per cent vs 1.14 per cent and 1.18 per cent for HbA1c ≥9.0 per cent).

In patients using insulin, adding empagliflozin reduced HbA1c by 0.6–0.7 per cent compared with placebo after 18 weeks; after 52–72 weeks, this reduction remained at about 0.4–0.6 per cent despite a small reduction in insulin dose, with a mean weight loss of 3–4kg.

**Adverse effects**
The adverse events associated with empagliflozin in clinical trials were typical of the SGLT2 inhibitors, notably including genital infections (4 per cent vs 1 per cent with placebo); the incidence of urinary tract infection was similar to that with placebo (8–9 per cent). Confirmed hypoglycaemic events were more frequent when empagliflozin was added to metformin plus a sulfonylurea (20 per cent with 10mg/day and 15 per cent with 25mg/day vs 12 per cent with placebo). Empagliflozin 25mg/day was associated with a higher incidence of hypoglycaemia than 10mg/day or placebo when added to insulin (with or without metformin and/or a sulfonylurea) at 18 weeks (28 per cent vs 20 and 21 per cent) but not at 78 weeks (36, 36 and 35 per cent). Severe hypoglycaemic events were rare.

**References**

**Declaration of interests**
Steve Chaplin has none to declare.

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**Place in therapy**

*Surya Rajeev and John Wilding*

Effective and well tolerated antihyperglycaemic drugs that decrease body weight and have a low risk of causing hypoglycaemia have a special place in the management of diabetes from the patient’s and clinician’s perspective.

SGLT2 inhibitors are a novel class of antihyperglycaemic agents that lower blood glucose by reducing renal glucose reabsorption and thereby inducing glycosuria. Energy loss in the urine translates to loss of body weight in clinical practice and due to its insulin-independent mode of action, these drugs can be used in the management of type 2 diabetes at any stage. Empagliflozin is the third SGLT2 inhibitor available in the UK. The European Medicines Agency (EMA) approved the use of empagliflozin in May 2014 at 10mg and 25mg doses as monotherapy (when metformin intolerant) or combination therapy with other agents including insulin (when glycaemic target not attained). Since the mechanism of action is based on renal glucose filtration, drugs in this class are not efficacious in people with moderate or severe renal impairment (CKD stage 3b, 4 and 5).

Empagliflozin has been shown to reduce HbA1c by 0.5–1 per cent (6–11mmol/mol; similar to other SGLT2 inhibitors). Compared to other oral hypoglycaemic agents, advantages are reduction in body weight (around 2kg) and systolic BP (around 5mmHg), with a low intrinsic risk of causing hypoglycaemia.1

Risk of hypoglycaemia was not increased when empagliflozin was used as monotherapy or combination therapy with metformin, pioglitazone or adjusted doses of insulin. An increased risk of hypoglycaemia when combined with a sulfonylurea has been noted similar to other antidiabetic drugs used in this combination. Though increased risk of UTI was reported with some phase 3 trials, meta-analysis showed increased incidence of genital tract infections only.1 Due to volume depletion associated with osmotic diuresis, this class of drugs should be used with caution in patients >75 years of age, patients with low BP and patients on loop diuretics. Other adverse effects are small increases in HDL and LDL cholesterol, and haematocrit, and small decrease in serum uric acid. Results from large ongoing trials are awaited to explain the long-term safety profile and cardiovascular outcomes.2,3

From available data, empagliflozin is well tolerated, improves glycaemia and has the additional advantage of reduction in body weight and systolic BP with no increased risk of hypoglycaemia, but increased risk of genital infections. Empagliflozin can be used as monotherapy in patients with intolerance to metformin (where weight loss is desirable) and in combination with other antidiabetic agents including insulin where weight loss would benefit other co-morbidities. NICE has recently approved empagliflozin (TA 336, March 2015) as dual therapy with metformin in patients who cannot take a sulfonylurea, in triple combinations with metformin plus a sulfonylurea or pioglitazone and in combination with insulin with or without other oral agents.

**References**

**Declaration of interests**
Surya Rajeev has none to declare. Professor Wilding has acted as a consultant, received institutional grants and given lectures on behalf of pharmaceutical companies including Boehringer-Ingelheim, AstraZeneca and Janssen.

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