Drugs (2014) 74:1769–1784
DOI 10.1007/s40265-014-0298-1

ADIS DRUG EVALUATION

Empagliflozin: A Review of Its Use in Patients with Type 2 Diabetes Mellitus

Lesley J. Scott

Published online: 2 October 2014
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Abstract Oral empagliflozin (Jardiance®), a sodium glucose cotransporter-2 (SGLT2) inhibitor, is a convenient once-daily treatment for adult patients with type 2 diabetes mellitus. By inhibiting reabsorption of glucose from the proximal tubules in the kidney via inhibition of SGLT2, empagliflozin provides a novel insulin-independent mechanism of lowering blood glucose. In several phase III trials (≤104 weeks' duration; typically 24 weeks' duration) and extension studies (typically ≥76 weeks' treatment), empagliflozin monotherapy or add-on therapy to other antihyperglycaemics, including insulin, improved glycaemic control and reduced bodyweight and systolic blood pressure in adult patients with type 2 diabetes. In a large phase III trial, as add-on therapy to metformin, empagliflozin was shown to be noninferior to glimepiride at 52 and 104 weeks and superior to glimepiride at 104 weeks, in terms of reductions in glycated haemoglobin level (primary endpoint). Empagliflozin was well tolerated by participants in these clinical trials, with most adverse events being mild or moderate in intensity. Empagliflozin treatment appeared to have no intrinsic risk of hypoglycaemia, although hypoglycaemia occurred more frequently when empagliflozin was coadministered with insulin and/or a sulfonylurea. With its insulin-independent mechanism of action, empagliflozin monotherapy or combination therapy with other antidiabetic drugs, including insulin, provides a useful addition to the therapeutic options for the management of type 2 diabetes. This article reviews the pharmacological properties and clinical use of empagliflozin in patients with type 2 diabetes.

Empagliflozin in type 2 diabetes mellitus: a summary

High-affinity, sodium glucose cotransporter-2 (SGLT2) inhibitor that results in increased urinary glucose excretion, thereby lowering blood glucose in an insulin-independent manner

As monotherapy or add-on therapy to other antihyperglycaemic drugs, including insulin, empagliflozin improves glycaemic control, reduces bodyweight and lowers BP compared with placebo

As add-on therapy to metformin, improvement in glycaemic control is noninferior to glimepiride at 52 weeks and superior to glimepiride at 104 weeks

Generally well tolerated and has a low intrinsic risk of hypoglycaemia

The manuscript was reviewed by: ***G. Dimitriadis***, 2nd Department of Internal Medicine, Research Institute and Diabetes Center, Athens University Medical School, Attikon University Hospital, Athens, Greece; ***H-U. Häring***, Department of Internal Medicine IV, University of Tübingen, Tübingen, Germany; ***Y. Hamamoto***, Medical Research Institute Kitano Hospital, Center for Diabetes and Endocrinology, Osaka, Japan.

L. J. Scott (✉)
Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand
e-mail: demail@springer.com

1 Introduction

Type 2 diabetes mellitus, which accounts for ≈95 % of cases of diabetes, is a chronic progressive disease resulting from dysregulation of glucose homeostasis [1, 2]. The

disease is characterized by impairment of pancreatic β-cell function and consequent insulin insufficiency, insulin resistance in peripheral tissues and abnormalities in the secretion of other islet hormones [1, 2]. With an estimated 382 million people affected by the disease in 2013 and a predicted 55 % increase in affected individuals by 2035, the prevalence of diabetes has reached epidemic proportions, which for the most part, reflects a growing ageing population and an increase in obesity worldwide [3]. Type 2 diabetes is associated with significant morbidity and mortality and, as a result, poses an ever increasing cost to society and the health payer. Indeed, in 2013, diabetes-related global health expenditure in adults aged 20–79 years was more than US$500 billion. Globally, there were approximately 4 million diabetes-related deaths in 2010 and several million individuals experience high morbidity associated with complications of the disease, including myocardial infarction, stroke, kidney failure, blindness and lower limb amputations [4, 5]. Poor glycaemic control in patients with diabetes is central to the risk of developing these microvascular and macrovascular complications; hence, achievement of glycaemic control [i.e. a glycated haemoglobin (HbA_{1c}) level of <7 %] is the primary target in the management of diabetes to prevent the onset and/or progression of these complications [4, 6].

Despite the availability of numerous classes of antihyperglycaemic drugs with complementary mechanisms of action that target several pathogenic processes associated with type 2 diabetes, many patients fail to achieve glycaemic control [1, 2, 6]. Hence, novel approaches are required to improve glycaemic control, with the majority of patients requiring combination therapy with at least two antihyperglycaemic drugs with complementary modes of action [6]. The prevention of glucose reabsorption from the proximal tubules in the kidney via inhibition of the high-capacity, low-affinity sodium glucose cotransporter-2 (SGLT2), which accounts for up to 90 % of glucose reabsorption, provides a novel insulin-independent mechanism of lowering blood glucose [7, 8].

Oral empagliflozin (Jardiance®) (Fig. 1) is the most recent SGLT2 inhibitor to be approved in the EU and USA for the treatment of adult patients with inadequately controlled type 2 diabetes and is in pre-registration elsewhere. This article reviews the pharmacology, therapeutic efficacy and tolerability of oral empagliflozin in the management of type 2 diabetes.

2 Pharmacodynamic Properties

Empagliflozin is a potent, highly selective SGLT2 inhibitor (dissociation equilibrium constant for SGLT2 57 nmol/L) [9]. As a consequence of SGLT2 inhibition, the drug inhibits reabsorption of filtered glucose in the proximal tubules of the kidneys and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion (UGE) and reducing blood glucose levels. Empagliflozin inhibited SGLT2 in a dose-dependent manner in in vitro studies, with a >2,500-fold higher selectivity for SGLT2 than for SGLT1; respective concentrations required to produce 50 % inhibition (IC_{50}) were 3.1 and 8,300 nmol/L. Moreover, this selectivity was markedly higher than those exhibited by other SGLT2 inhibitors, including dapagliflozin (>1,200-fold selectivity for SGLT2 vs. SGLT1) and canagliflozin (>250-fold selectivity). SGLT1 primarily acts in the small intestine to absorb glucose and galactose, but also acts in the distal segment of the proximal tubule to reabsorb residual glucose not taken up by SGLT2. Empagliflozin also showed less selectivity for other SGLTs than for SGLT2 (IC_{50} values for SGLT1, SGLT4, SGLT5 and SGLT6 ranged from 1,100 to 11,000 nmol/L), with no relevant inhibition of glucose-transporter-1 [9].

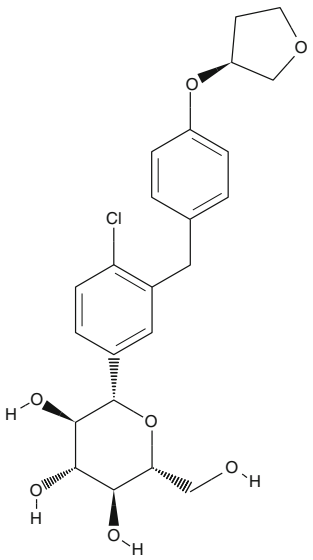

Fig. 1 Chemical structure of empagliflozin

In single-dose, dose-ranging studies in healthy Caucasian [10] and Japanese [11] volunteers, a dose-dependent increase in glucosuria was observed with empagliflozin doses of ≤100 mg. With empagliflozin 10 and 25 mg doses, the mean total amounts of UGE in the 24-h post-dose period were 47.9 and 56.5 g compared with 0.06 g in the placebo group [10], with similar results observed in the Japanese study [11]. Reabsorption of glucose was inhibited by approximately 40–60 % after single doses of empagliflozin 25–100 mg and by <40 % with empagliflozin doses of ≤10 mg [10, 11], with inhibition of reabsorption plateauing at approximately 100 mg [10]. Irrespective of the empagliflozin dose, there was no

change in plasma glucose concentrations in healthy volunteers [10, 11].

In a placebo-controlled study in patients with type 2 diabetes ($n = 16$–30/group) [12], mean cumulative UGE increased to a significantly ($p < 0.0001$) greater extent on day 1 in the empagliflozin 10, 25 and 100 mg groups (by 74, 90 and 81 g, respectively) than in the placebo group (minimal change in UGE), representing an approximately 11-fold to 18-fold increase from baseline in UGE on day 1 in empagliflozin groups. Significant increases in UGE in empagliflozin groups were maintained throughout the study ($p < 0.0001$ at day 27 and day 28). Glucose reabsorption was inhibited by 36–45 % on day 1 and by 36–48% on day 27 [12]. These data are supported by results from an 8-day, single-dose study [13] and a 4-week, multiple-dose, Japanese study [14] in adult patients with type 2 diabetes.

In a 4-week, single- and multiple dose study in 66 patients with type 2 diabetes, treatment with empagliflozin 25 mg once daily induced glucosuria in both the fasted and fed state [15]. Empagliflozin-induced glucosuria after single and multiple doses resulted in improvements in β-cell function and insulin sensitivity, with reductions in insulin secretion and tissue glucose disposal and increases in endogenous glucose production leading to reductions in fasting and postprandial glycaemia [15].

After 4 weeks of empagliflozin 10–100 mg once daily, there were significant ($p < 0.05$) reductions in fasting plasma glucose (FPG) and mean daily plasma glucose (MDG) levels from baseline compared with placebo in patients with type 2 diabetes, except for MDG levels in empagliflozin 10 mg group [12]. However, changes from baseline (mean baseline HbA_{1c} ≤7.5 % in all groups) in HbA_{1c} levels did not reach statistical significance in this short-term study (mean change −0.22 to −0.36 % in empagliflozin groups and −0.18 % in the placebo group) [12]. These data are supported by a 4-week, double-blind, Japanese study in adult patients with type 2 diabetes in which mean adjusted reductions from baseline in FPG, MDG and HbA_{1c} were all significantly ($p < 0.01$) greater with empagliflozin 10 and 25 mg once daily than with placebo [14]. The efficacy of empagliflozin in improving glycaemic control in patients with inadequately controlled type 2 diabetes participating in large clinical trials of ≥12 weeks' duration is discussed in Sect. 4, as is its efficacy in improving blood pressure (BP) and bodyweight.

There were no clinically relevant effects of single doses of empagliflozin 25 mg (therapeutic dose) and 200 mg (supratherapeutic dose) on the heart-rate corrected QT interval in healthy adult volunteers in a thorough, placebo- and active-comparator controlled QT study [16].

3 Pharmacokinetic Properties

The pharmacokinetic profile of oral empagliflozin in adult patients with type 2 diabetes [12–14] showed no clinically relevant difference from that in healthy volunteers [10, 11, 17], including in Japanese studies [11, 14]. An overview of the steady-state pharmacokinetic profile of empagliflozin in Caucasian patients (98 % of enrolled patients) is presented in Table 1 [12, 13].

Exposure to empagliflozin increased in a dose-proportional manner following multiple once-daily doses (1–100 mg) in patients with type 2 diabetes [12–14]. The drug was rapidly absorbed [12–14], with peak plasma concentrations (C_{max}) attained within 2 h after multiple doses of empagliflozin 10 and 25 mg/day (Table 1). Steady state was attained after 5–6 days [12, 13]. In healthy volunteers, there were no clinically relevant effects of food on exposure to empagliflozin [17, 18].

The apparent steady-state volume of distribution of empagliflozin was estimated to be 73.8 L, based on a population pharmacokinetic study [18]. Following a single-radiolabelled dose of empagliflozin, approximately 37 % of the drug was partitioned in red blood cells and 86 % was bound to plasma protein [18].

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the 5′-uridine diphosphoglucuronosyltransferases (UGT) 1A3, 1A8, 1A9 and 2B7 [18]. No major metabolites of empagliflozin were detected in human plasma and systemic exposure of each metabolite was <10 % of total drug-related material. Empagliflozin is a substrate for organic anion-transporter polypeptide (OATP) B1 and B3, organic anion transporter 3 (OAT3), P-glycoprotein and breast cancer resistance protein, but not for OAT1 and organic cationic transporter 2 [18].

Approximately 41 % of the drug-related radioactivity was eliminated in the faeces, the majority as unchanged drug, and approximately 54 % was eliminated in the urine,

Table 1 Mean steady-state pharmacokinetic values with recommended dosages of oral empagliflozin in patients with type 2 diabetes mellitus [12, 13]

Parameter	EMP 10 mg od	EMP 25 mg od
C_{max} (nmol/L)	259–283	630–687
Median t_{max} (h)	1.5	1.5–2.0
AUC_{τ} (nmol·h/L)	1,870–2,030	4,740–4,990
$t_{½}$ (h)	13.2–14.3	10.7–13.3
$CL_{R\tau}$ (mL/min)	34.4–37.0	23.5–36.2

AUC_{τ} area under the plasma concentration-time curve over the dosing interval, *C_{max}* maximum plasma concentration, *$CL_{R\tau}$* renal clearance over the dosing interval, *EMP* empagliflozin, *od* once daily, *t_{max}* time to C_{max}, *$t_{½}$* terminal elimination half-life

of which about 50 % was unchanged drug [18]. At steady-state, the mean elimination half-life with empagliflozin 10 or 25 mg/day ranged from 10.7 to 14.3 h in patients with type 2 diabetes [12, 13]. Consistent with that half-life, up to 23 % accumulation of empagliflozin occurred following multiple doses [12]. Steady-state mean renal clearance of empagliflozin over 24 h (i.e. the dosing interval) with empagliflozin 2.5–100 mg/day ranged from 23.5 to 34.4 mL/min [13] and that with empagliflozin 10–100 mg/day ranged from 36.2 to 37.0 mL/min [12].

3.1 Potential Drug-Drug Interactions

In general, based on studies in healthy volunteers (unless stated otherwise), empagliflozin was not associated with drug-drug interactions when concomitantly administered with other glucose lowering drugs or with cardiovascular drugs commonly used in patients with type 2 diabetes (as reviewed by Scheen [19]). There were no clinically relevant pharmacokinetic interactions between empagliflozin and linagliptin [20], sitagliptin [21], metformin [22], pioglitazone [18] or glimepiride [23]. There were also no clinically relevant pharmacokinetic interactions between empagliflozin and verapamil [24], ramipril [24], digoxin [24], warfarin [25], diuretic agents (hydrochlorothiazide and torasemide; study in patients with type 2 diabetes) [26] or simvastatin [27].

There were no clinically relevant drug-drug interactions when empagliflozin was coadministered with the OATP1B1/1B3 and OAT3 inhibitor gemfibrozil, with the OATP1B1/1B3 inhibitor rifampicin or with the OAT3 and UGT inhibitor probenecid [28].

In healthy premenopausal women, empagliflozin had no effect on the pharmacokinetics of the combined oral contraceptive ethinylestradiol/levonorgestrel, based on bioequivalence criteria [29].

Empagliflozin does not inhibit, inactivate or induce cytochrome P450 (CYP450) enzymes or UGT1A1, based on in vitro studies [18]. Therefore, pharmacokinetic interactions involving the major CYP450 enzymes or UGT1A1 with empagliflozin and concomitantly administered substrates of these enzymes are considered unlikely. Coadministration of empagliflozin with known inducers of UGT enzymes (e.g. phenytoin, carbamazepine) should be avoided due to the potential risk of reduced efficacy; no formal studies of the effect of UGT induction on empagliflozin have been conducted [18].

3.2 In Special Patient Populations

Gender, body mass index (BMI) and age had no clinically relevant effect on the pharmacokinetics of empagliflozin, based on a population pharmacokinetic analysis [18, 30]. Exposure to empagliflozin was estimated to be 13.5 % higher in Asians with a BMI of 25 kg/m^2 than in non-Asians with a BMI of 25 kg/m^2, based on a population pharmacokinetic analysis [18]. No pharmacokinetic studies have been conducted in paediatric patients [18].

In patients with or without type 2 diabetes who had mild [estimated glomerular filtration rate (eGFR) 60–89 mL/min/1.73 m^2], moderate (eGFR 30–59 mL/min/1.73 m^2) or severe renal impairment (eGFR <30 mL/min/1.73 m^2) and those with end stage renal disease (ESRD) requiring dialysis, systemic exposure to empagliflozin after a single 50 mg dose was moderately increased (by 18–66 %) compared with that in patients with type 2 diabetes and normal renal function (eGFR >90 mL/min/1.73 m^2) [31]. Increased systemic exposure was attributed to decreased renal clearance of empagliflozin as the degree of renal impairment increased [31]. See Sect. 6 for dosage recommendations for empagliflozin in patients with renal impairment.

There were no clinically relevant effects of mild (Child-Pugh class A), moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C) on the pharmacokinetics of empagliflozin compared with healthy volunteers following single 50 mg doses of empagliflozin [32]. The overall increase in empagliflozin exposure in patients with varying degrees of hepatic impairment was less than twofold and, for the most part, reflected an increase in area under the plasma concentration-time curve values rather than an increase in C_{max} values [32]. Clinical experience in patients with severe hepatic impairment is limited and therefore, empagliflozin is not recommended in this patient population [18].

4 Therapeutic Efficacy

The efficacy of oral empagliflozin, as monotherapy (Sect. 4.1) or add-on therapy to oral antidiabetic drugs (OADs; Sects. 4.2, 4.3) or subcutaneous insulin (Sect. 4.4), was investigated in several randomized, double-blind, multinational (except for Japanese trials [33–35]), phase II [33, 36–38] or III [39–44] trials in adult patients with inadequately controlled type 2 diabetes. The longer term efficacy of empagliflozin has been evaluated in a phase III trial (104 weeks' duration) [43] and extension studies (≥90 weeks' empagliflozin treatment) [34, 45–48] of shorter-term phase II and III trials. Discussion focuses on data from phase III trials in patients receiving recommended dosages of empagliflozin (i.e. 10 or 25 mg once daily; see Sect. 6). Inadequately controlled type 2 diabetes was typically defined as an HbA_{1c} level of 7–10 % at baseline. Major exclusion criteria in phase III trials were generally similar across trials and included uncontrolled

hyperglycaemia (i.e. plasma glucose >13.3 mmol/L after an overnight fast during the run-in period, confirmed by a second measurement) and the presence of significant comorbidities, including renal insufficiency/impairment (eGFR of <30 mL/min/1.73 m^2 [40, 41, 44], <50 mL/min/1.73 m^2 [39] or <60 mL/min/1.73 m^2 [33, 42, 43]).

In addition, the efficacy of empagliflozin has been evaluated in double-blind, placebo-controlled, multinational, phase III studies in adult patients with inadequately controlled type 2 diabetes and hypertension (as monotherapy; Sect. 4.5.1) [49] and as add-on therapy in adult patients with inadequately controlled type 2 diabetes and chronic kidney disease (CKD; Sect. 4.5.2) [50].

The primary endpoint in all trials was the change from baseline in HbA_{1c} level at study end and/or at a prespecified earlier time point. The co-primary endpoint in a phase III trial in patients with type 2 diabetes and hypertension was the change in mean 24-h systolic BP (SBP; assessed using ambulatory blood pressure monitoring) from baseline to study end at 12 weeks [49]. Efficacy analyses were conducted in the full analysis set populations, which typically included all patients who received ≥1 dose of study drug and had a baseline HbA_{1c} assessment.

Within each trial, there were no significant differences between treatment groups in the demographics and clinical characteristics of patients at baseline. Exercise and diet counselling was part of the study protocols. A conversion factor of 0.05551 was used to convert FPG values from mg/dL to mmol/L. Some data are currently only available as abstract or poster presentations [34, 35, 38, 46–48].

4.1 Monotherapy

Monotherapy with empagliflozin 10 or 25 mg once daily provided significantly greater improvements in glycaemic control than placebo at study end in 12-week, dose-ranging, phase II trials [33, 37], including in a Japanese study (Table 2) [33], and in a 24-week, phase III trial [39] (Table 2). There were significantly ($p < 0.001$) greater reductions from baseline in HbA_{1c} levels with empagliflozin treatment than with placebo (primary endpoint) and, in general, a significantly ($p < 0.05$) greater proportion of patients in empagliflozin groups than in placebo groups achieved target HbA_{1c} levels of <7 % at study end (Table 2) [33, 39]. Other secondary endpoints also favoured empagliflozin treatment over placebo, including adjusted mean changes from baseline in FPG levels, bodyweight and systolic blood pressure (SBP) at study end (Table 2).

In the phase III study, there were no significant differences between the empagliflozin groups and the sitagliptin group in adjusted mean changes from baseline in HbA_{1c} levels or the proportion of patients achieving a target HbA_{1c} level of <7 % at 24 weeks (Table 2) [39]. In patients with a baseline HbA_{1c} level of ≥8.5 % (mean ≈9.1 % in all groups; $n = 45$–54/group), once-daily empagliflozin 10 or 25 mg improved glycaemic control to greater extent than sitagliptin at 24 weeks (adjusted mean change −1.44 and −1.43 vs. −1.04 %; both $p < 0.02$), with all active treatments being significantly ($p < 0.0001$) more effective than placebo (adjusted mean increase 0.01 %). In patients with a baseline HbA_{1c} level of <8.5 % (mean ≈7.5 % in all groups), there were no significant differences in improvements in HbA_{1c} levels between the empagliflozin and sitagliptin groups, with both active treatments being more effective than placebo ($p < 0.0001$ for all groups). With empagliflozin, improvements in HbA_{1c} level were significantly ($p < 0.0001$) greater in patients with an HbA_{1c} level of ≥8.5 % at baseline than in those with an HbA_{1c} level of <8.5 % at baseline. At study end, adjusted mean changes from baseline in bodyweight (Table 2), waist circumference ($p < 0.0001$ vs. sitagliptin and placebo) and in the proportion of patients with a >5 % reduction in bodyweight from baseline ($p < 0.0001$ vs. sitagliptin and placebo) significantly favoured empagliflozin therapy. Empagliflozin recipients also experienced significantly greater improvements in SBP than sitagliptin recipients at study end (Table 2). In patients who had uncontrolled BP at baseline, a greater proportion of empagliflozin 10 and 25 mg recipients achieved controlled BP [i.e. SBP/diastolic BP (DBP) <130/80 mmHg] at study end than sitagliptin recipients (27 and 31 vs. 18 %), although significance ($p = 0.011$) was only reached with empagliflozin 25 mg; both empagliflozin dosages were significantly more effective than placebo (13 %; $p \leq 0.006$) [39].

In patients with poor glycaemic control at baseline, open-label treatment with empagliflozin 25 mg once daily improved glycaemic control over 24 weeks (Table 2) [39].

Clinically meaningful improvements in glycaemic control and other endpoints with empagliflozin monotherapy were sustained in a 40-week extension study [34] of a 12-week Japanese phase II trial [33], a 78-week extension study [45] of a 12-week, multinational, phase II trial [37] and a ≥52 week extension study [48] of a 24-week, multinational, phase III trial [39]. For example, in the phase III extension study, after ≥76 weeks of empagliflozin 10 or 25 mg once daily ($n = 224$ in both groups), improvements in glycaemic control, bodyweight and SBP were maintained and were significantly greater in the empagliflozin groups than in the placebo group ($n = 228$); patients continued to receive randomized study drug until all patients had been treated for ≥ 76 weeks [48]. At 76 weeks, the adjusted mean between-group differences for the empagliflozin 10 and 25 mg groups versus the placebo group for changes from baseline in HbA_{1c} were

Table 2 Efficacy of empagliflozin monotherapy in patients with type 2 diabetes mellitus. Results from double-blind, multicentre trials at study end in the full analysis set

Study (duration; weeks)	Regimen (mg od; oral)	No. of pts	Adjusted mean change from baseline at study end (mean baseline)				% pts at target HbA_{1c} <7 %
			HbA_{1c} [a] (%)	FPG (mmol/L)	Bodyweight (kg)	SBP (mmHg)	
Roden et al. [39] (24) (EMPA-REG MONO)	EMP 10	224	−0.66**** (7.9)	−1.08****††† (8.5)	−2.26****††† (78.4)	−2.9*† (133.0)	35.3 (OR 4.12****)
	EMP 25	224	−0.78**** (7.9)	−1.36****††† (8.5)	−2.48****††† (77.8)	−3.7**†† (129.9)	43.6 (OR 6.15****)
	Sitagliptin 100	223	−0.66**** (7.9)	−0.38**** (8.2)	+0.18* (79.3)	+0.5 (132.5)	37.5 (OR 4.76****)
	PL	228	+0.08 (7.9)	+0.65 (8.6)	−0.33 (78.2)	−0.3 (130.4)	12.0
	EMP 25[b] (open-label)	87	−3.70 (11.5)	−4.86 (12.8)	−2.43 (80.7)	−4.0 (129.5)	NR
Kadowaki et al. [33][c] (12)	EMP 10	109	−0.40*** (7.9)	−1.40*** (8.7)	−2.6*** (68.1)	−5.6** (127.8)	19***
	EMP 25	109	−0.65***(7.9)	−1.87*** (8.7)	−2.9*** (68.3)	−4.6* (126.5)	32***
	PL	109	+0.30 (7.9)	+0.22 (8.7)	−0.9 (69.0)	−1.4 (131.1)	3

EMP empagliflozin, *FPG* fasting plasma glucose, *HbA_{1c}* glycated haemoglobin, *NR* not reported, *od* once daily, *OR* odds ratio (vs. PL), *PL* placebo, *pts* patients, *SBP* systolic blood pressure

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ vs. PL, † $p < 0.01$, †† $p < 0.001$, ††† $p < 0.0001$vs. sitagliptin

[a] Primary endpoint in double-blind treatment groups

[b] Pts with an HbA_{1c} level of >10 % at screening received open-label EMP 25 mg od for 24 weeks (i.e. nonrandomized group)

[c] Dose-ranging study; only dosages of EMP recommended in the EU and USA are tabulated

−0.78 and −0.89 % (both $p < 0.001$), those for changes in bodyweight were −1.8 and −2.0 kg (both $p < 0.001$) and those for changes in SBP were −3.4 and −3.4 mmHg (both $p < 0.01$). At this time point, adjusted mean between-group differences for the empagliflozin 10 and 25 mg groups versus the sitagliptin group ($n = 223$) for changes from baseline in HbA_{1c} were −0.12 (not significant) and −0.22 % ($p < 0.01$), those for changes in bodyweight were −2.3 and −2.6 kg (both $p < 0.001$) and those for changes in SBP were −3.7 and −3.8 mmHg (both $p < 0.001$) [48].

4.2 Add-On Therapy to Metformin

In a phase III trial in patients with inadequately controlled type 2 diabetes despite metformin therapy, add-on once-daily empagliflozin 10 or 25 mg was significantly more effective than add-on placebo in improving glycaemic control, as determined by adjusted mean changes in HbA_{1c} and FPG and the percentage of patients achieving a target HbA_{1c} level of <7 % at 24 weeks (Table 3) [44]. Patients receiving empagliflozin 10 and 25 mg once daily also achieved significantly greater improvements from baseline in bodyweight (Table 3), SBP (Table 3) and diastolic BP (DBP; −2.0 and −1.6 vs. 0.0 mmHg; $p < 0.05$; baseline DBP 78–80 mmHg) than placebo recipients [44].

These data are supported by results from a 12-week, dose-ranging, phase II trial, in which empagliflozin 10 or 25 mg once daily ($n = 71$ and 70) was administered as add-on therapy to metformin ≥1,500 mg/day [36]. At study end, add-on empagliflozin was significantly ($p < 0.001$) more effective than add-on placebo in improving glycaemic control and bodyweight, with significantly ($p < 0.001$) more empagliflozin recipients achieving a target HbA_{1c} level of ≤7 %. In a 78-week, open-label, extension study [45] of this trial, patients who had been randomized to empagliflozin 10 or 25 mg/day as add-on therapy to metformin in the initial double-blind trial continued to receive the same dosage of add-on empagliflozin. Those randomized to add-on empagliflozin 1, 5 or 50 mg/day or placebo were re-randomized to open-label, add-on empagliflozin 10 or 25 mg/day and patients who received sitagliptin as add-on therapy to metformin in the initial study continued with this regimen. Improvements in glycaemic control were sustained in the add-on empagliflozin groups, with clinically meaningful improvements from the extension baseline HbA_{1c} level (adjusted mean change −0.34 and −0.63 %; baseline 7.9 % in both groups) and FPG levels (adjusted mean change −1.17 and −1.78 mmol/L; baseline 9.8 and 9.9 mmol/L) in the empagliflozin 10 and 25 mg groups after 90 weeks ($n = 137$ and 139 evaluable). Adjusted mean changes in bodyweight at the end of the extension phase were −3.1 and −4.0 kg in the add-on empagliflozin 10 mg and 25 mg groups, with

corresponding changes in SBP of −3.3 and −3.0 mmHg [45].

As add-on therapy to metformin, empagliflozin 25 mg/day was non-inferior to glimepiride 1–4 mg/day at 52 and 104 weeks, and superior to glimepiride at 104 weeks, in terms of adjusted mean changes in HbA_{1c} level at these primary time points in a phase III trial (Table 3) [43]. At 104 weeks, add-on empagliflozin was non-inferior to (all $p < 0.001$), but not significantly superior to, add-on glimepiride, irrespective of whether patients received glimepiride titration of ≥2, ≥3 or 4 mg/day. At both 52 and 104 weeks, adjusted mean changes in FPG, bodyweight and SBP were also significantly greater in the add-on empagliflozin group than in the add-on glimepiride group, with bodyweight and SBP increasing from baseline in the glimepiride group (Table 3). Adjusted mean changes from baseline in DBP also significantly ($p < 0.0001$) favoured add-on empagliflozin over add-on glimepiride at 52 (−1.9 vs. +0.9 mmHg; baseline 79.5 and 79.4 mmHg) and 104 weeks (−1.8 vs. +0.9 mmHg) [43].

In the mixed meal tolerance test substudy of this phase III trial [43], add-on empagliflozin was associated with significantly greater reductions in 2-h postprandial plasma glucose than add-on glimepiride at 104 weeks (2.58 vs. 1.80 mmol/L; $p < 0.05$; baseline 14.00 and 14.04 mmol/L; $n = 116$ and 120), but not at 52 weeks (2.76 vs. 2.02 mmol/L; baseline 13.93 and 14.07 mmol/L; $n = 112$ and 117). There were no significant between-group differences at 52 and 104 weeks for changes from baseline in MDG in the MDG substudy, based on 8-point self-monitored glucose levels [43].

4.3 Add-On Therapy to Other Oral Antihyperglycaemic Drugs

As add-on therapy to metformin plus a sulfonylurea, once-daily empagliflozin 10 or 25 mg was significantly more effective than add-on placebo in reducing HbA_{1c} levels at 24 weeks (Table 3) [40]. Furthermore, add-on empagliflozin significantly (all $p < 0.01$) reduced HbA_{1c} levels compared with add-on placebo, irrespective of whether patients had normal renal function (eGFR ≥ 90 mL/min/1.73 m^2), mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2) or moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2). Secondary endpoints also favoured add-on empagliflozin over add-on placebo, including adjusted mean changes in FPG, bodyweight and SBP (Table 3). There were no significant differences in terms of reductions from baseline in DBP at study end. Significantly more patients in the empagliflozin 10 and 25 mg groups than in the placebo group achieved a >5 % reduction in bodyweight (27.6 and 23.6 vs. 5.8 %; respective odds ratios vs. placebo of 6.36 and 5.19; both $p < 0.001$), with reductions in bodyweight associated with significant reductions in waist circumference compared with placebo (1.46 and 1.48 vs. 0.31 cm; both $p = 0.003$) [40].

In a double-blind extension study (≥52 weeks' duration) [47] of this trial [40], after ≥76 weeks of empagliflozin 10 or 25 mg once daily as add-on therapy to metformin plus a sulfonylurea ($n = 225$ and 216), improvements in glycaemic control, bodyweight and SBP were maintained and were significantly greater in the empagliflozin groups than in the add-on placebo group ($n = 225$); patients continued to receive randomized study drug until all patients had been treated for ≥76 weeks. At 76 weeks, the adjusted mean between-group differences for the empagliflozin 10 and 25 mg groups versus the placebo group for changes in HbA_{1c} were −0.72 and −0.69 % (both $p < 0.001$), those for changes in bodyweight were −1.8 and −1.6 kg (both $p < 0.001$) and those for changes in SBP were −2.2 and −2.1 mmHg (both $p < 0.05$) [47].

In patients with inadequately controlled type 2 diabetes despite treatment with pioglitazone with or without metformin, add-on empagliflozin therapy significantly improved glycaemic control at 24 weeks compared with add-on placebo, as assessed by primary and secondary endpoints (Table 3) [41]. Mean improvements from baseline in DBP were also significantly ($p \leq 0.014$) greater in the add-on empagliflozin 10 and 25 groups than in the add-on placebo group at study end (−1.49 and −2.21 vs. 0.29 mmHg). Significantly more patients in the empagliflozin 10 mg group than in the placebo group who had uncontrolled BP at baseline achieved controlled BP at study end (38 vs. 22 %; $p = 0.011$), with no significant difference between the empagliflozin 25 mg and placebo groups (33 vs. 22 %). At 24 weeks, significantly more patients in the empagliflozin 10 and 25 mg groups than in the placebo group had a >5 % reduction from baseline in bodyweight (18.8 and 13.7 vs. 5.5 %; both $p \leq 0.01$) and mean changes in waist circumference were greater in empagliflozin groups than in the placebo group (−1.67 and −0.92 vs. +0.20 cm; both $p < 0.05$) [41].

In a double-blind extension study (≥52 weeks' duration) [46] of this trial [41], improvements in glycaemic control, bodyweight and SBP were maintained after ≥76 weeks of add-on empagliflozin 10 or 25 mg once daily ($n = 165$ and 168; add-on to pioglitazone ± metformin); patients continued to receive randomized study drug until all patients had been treated for ≥76 weeks) [46]. At 76 weeks, the respective adjusted mean differences between the add-on empagliflozin 10 and 25 mg groups ($n = 165$ and 168) and the add-on placebo group ($n = 165$) significantly ($p < 0.001$) favoured add-on empagliflozin for changes in HbA_{1c} (−0.59 and −0.69 %;

Table 3 Efficacy of add-on empagliflozin in patients with inadequately controlled type 2 diabetes mellitus in double-blind, multinational, phase III trials at study end in the full analysis set

Study [trial name; duration (weeks)]	Regimen (mg od)	No. of pts	Adjusted mean change from BL at study end (mean BL)				% pts at target HbA_{1c} <7 %[a]
			HbA_{1c}[b] (%)	FPG (mmol/L)	Bodyweight (kg)	SBP (mmHg)	
Add-on to oral MET							
Häring et al. [44]	EMP 10 + MET[c]	217	−0.70*** (7.9)	−1.11*** (8.6)	−2.08*** (81.6)	−4.5*** (129.6)	38***
(EMPA-REG MET; 24)	EMP 25 +MET[c]	213	−0.77*** (7.9)	−1.24*** (8.3)	−2.46*** (82.2)	−5.2*** (130.0)	39***
	PL + MET[c]	207	−0.13 (7.9)	+0.35 (8.7)	−0.45 (79.7)	−0.4 (128.6)	13
	EMP 25 + MET[c] (ol)[d]	69	−3.23 (11.1)	−3.02 (11.3)	−1.91 (85.1)	−2.4 (126.2)	6
Ridderstrale et al. [43][e]	EMP 25 + MET[c]	765	−0.73 NI[f]; −0.66 NI[f] SUP[f] (7.9)	−1.08†; −0.85† (8.3)	−3.2†; −3.1† (82.5)	−3.6†; −3.1† (133.4)	39; 34
(EMPA-REG H2H-SU; 104)	GLIM 1–4 + MET[c]	780	−0.66; −0.55 (7.9)	−0.48; −0.17 (8.3)	+1.6; +1.3 (83.0)	+2.2; +2.5 (133.5)	39; 31
Add-on to other oral antidiabetic drugs							
Häring et al. [40]	EMP 10 + MET[c] + SU[g]	225	−0.82*** (8.1)	−1.29*** (8.4)	−2.16*** (77.1)	−4.1** (128.7)	26 (OR 3.9***)
(EMPA-REG METSU; 24)	EMP 25 + MET[c] + SU[g]	216	−0.77*** (8.1)	−1.29*** (8.7)	−2.39*** (77.5)	−3.5* (129.3)	32 (OR 5.2***)
	PL + MET[c] + SU[g]	225	−0.17 (8.2)	+0.31 (8.4)	−0.39 (76.2)	−1.4 (128.8)	9
	EMP 25 + MET[c] + SU[g] (ol)[d]	101	−2.89[h] (11.2)	−3.02[h] (11.1)	−1.76[h] (76.4)	−4.3[h] (126.4)	9
Kovacs et al. [41]	EMP 10 + PIO[i] ± MET[c]	165	−0.59*** (8.1)	−0.94*** (8.4)	−1.62*** (78.0)	−3.1*** (126.5)	24***
(EMPA-REG PIO; 24)	EMP 25 + PIO[i] ± MET[c]	168	−0.72*** (8.1)	−1.22*** (8.4)	−1.47*** (78.9)	−4.0*** (125.9)	30***
	PL + PIO[i] ± MET[c]	165	−0.11 (8.2)	+0.36 (8.4)	+0.34 (78.1)	+0.7 (125.7)	8
Add on to subcutaneous insulin							
Rosenstock et al. [42]	EMP 10 + INS[j]	186	−0.94***[k] (8.4); −1.18*** (8.4)	−1.32* (8.8)	−1.95*** (96.7)	−3.4 (134.2)	31**
(EMPA-REG MDI; 52)	EMP 25 + INS[j]	189	−1.02***[k] (8.3); −1.27*** (8.4)	−1.43** (8.3)	−2.04*** (95.9)	−3.8 (132.9)	42***
	PL + INS[j]	188	−0.50[k] (8.3); −0.81 (8.3)	−0.63 (8.4)	+0.44 (95.5)	−2.9 (132.6)	21

BL baseline, *EMP* empagliflozin *FPG* fasting plasma glucose, *GLIM* glimepiride, *HbA_{1c}* glycated haemoglobin, *INS* insulin, *MET* metformin, *NI* non-inferiority shown ($p < 0.0001$ vs. GLIM), *od* once daily, *ol* open-label, *OR* odds ratio (vs. PL), *PIO* pioglitazone, *PL* placebo, *pts* patients, *SBP* systolic blood pressure, *SU* sulfonylurea, *SUP* superiority shown ($p < 0.05$ vs. GLIM)

* $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs. PL group; † $p < 0.0001$ vs. GLIM group

[a] Assessed in pts with an HbA_{1c} of ≥7 % at BL

[b] Primary endpoint in double-blind treatment groups

[c] MET ≥1,500 mg/day, maximum tolerated dosage or maximum dosage according to label [40, 41, 44]; not specified [43]

[d] Pts with a BL HbA_{1c} of >10 %; nonrandomized group

[e] Results data are presented as 52-week data; 104-week data. Both were primary timepoints for the primary endpoint

[f] NI criterion was a one-sided significance level of 1.25 % and SUP criterion was a two-sided significance level of 2.5 %

[g] SU ≥50 % of the maximum recommended dosage or maximum tolerated dosage or maximum dosage according to local label

[h] Mean change

[i] PIO ≥30 mg/day or maximum tolerated dosage or maximum dosage according to local label; ≈25 % of pts in each group received PIO without MET

[j] Dose to remain within 10 % of dose at randomization for first 18 weeks; then to target FPG levels for weeks 19–40; and for week 41–52, the dose was to remain within 10 % of week 40 dose

[k] 18-week data, which was the primary time point for HBA_{1c} changes from BL; all other data are for changes at 52 weeks analysed in full analysis set pts who completed 52 weeks therapy

baseline 8.1–8.2 % in all groups) and bodyweight (−2.0 and −1.7 kg; baseline 78–79 kg in all groups). Mean adjusted reductions in SBP from baseline to 76 weeks were clinically meaningful and, in the add-on empagliflozin 25 mg group, were significantly greater than in the add-on placebo group (between-group difference −3.7 mmHg; $p < 0.01$) [46].

In a 52-week, randomized, parallel-group, safety study in Japanese patients with inadequately controlled type 2 diabetes, add-on empagliflozin 10 or 25 mg once daily, effectively improved glycaemic control in patients receiving background therapy with a sulfonylurea ($n = 273$), biguanide ($n = 133$), thiazolidinedione ($n = 273$), α-glucosidase inhibitor ($n = 139$), dipeptidyl peptidase-4 (DPP-4) inhibitor ($n = 139$) or a meglitinide ($n = 140$) [35]. At 52 weeks, adjusted mean changes from baseline in HbA_{1c} ranged from −0.77 to −1.00 % across the treatment groups (baseline HbA_{1c} 7.5–8.1 %). Efficacy was a secondary endpoint; no further design details or results were reported in the abstract presentation [35].

4.4 Add-On Therapy to Insulin

Empagliflozin 10 or 25 mg once daily, as add-on therapy to basal insulin, significantly ($p < 0.001$) improved glycaemic control compared with add-on placebo, as assessed by adjusted mean reductions in HbA_{1c} levels at 18 (primary time point and endpoint) and 52 weeks in a phase III trial in obese patients with inadequately controlled type 2 diabetes (Table 3) [42]. Significantly more patients in the add-on empagliflozin group than in the add-on placebo group achieved a target HbA_{1c} level of ≤7 % at 52 weeks (Table 3). There were also significant improvements in adjusted mean changes in FPG levels and bodyweight with add-on empagliflozin compared with add-on placebo at 52 weeks, with no significant between-group differences for changes in SBP (Table 3). At this time point, there was also a significant ($p < 0.01$) reduction from baseline in the daily basal insulin dose in the empagliflozin 10 and 25 mg groups compared with the placebo group (+1.3 and −1.1 vs. +10.2 IU/day); respective mean baseline doses were 89.9, 92.9 and 93.1 IU/day [42].

These data are supported by results from a double-blind, multinational, phase II trial [38, 51]. Empagliflozin 10 or 25 mg once daily, as add-on therapy to basal insulin, significantly ($p < 0.001$) improved glycaemic control compared with add-on placebo, as assessed by adjusted mean reductions in HbA_{1c} levels at week 18 (0.57 and 0.71 vs. 0.01 %; primary endpoint and time point; baseline 8.1–8.3 %) and 78 (0.48 and 0.64 vs. 0.02 %) [38]. There were also significant ($p < 0.01$) improvements in adjusted mean changes in FPG levels and bodyweight in both empagliflozin groups compared with the placebo group at 78 weeks, with a significant reduction in SBP in the empagliflozin 10 mg group compared with placebo. At 52 weeks, adjusted mean changes from baseline in daily insulin dose were significantly lower in the empagliflozin 10 and 25 mg groups than in the placebo group (+1.3 and −1.1 vs. +10.2 IU/day; both $p < 0.01$); respective baseline mean daily doses were 90.4, 89.4 and 99.5 IU/day [38].

4.5 Use in Special Patient Populations

4.5.1 Patients with Hypertension

A 12-week, double-blind, multinational phase III trial (EMPA-REG BP) evaluated the efficacy of empagliflozin 10 or 25 mg once daily in patients with inadequately controlled type 2 diabetes (i.e. an HbA_{1c} level of 7–10 %) and hypertension (mean seated office SBP 130–159 mmHg) [49]. Patients had to be antidiabetic treatment-naive [no OADs, GLP-1 analogue or insulin treatment for ≥12 weeks (≥16 weeks for pioglitazone) prior to randomization] or treatment-experienced [OADs or subcutaneous antidiabetic drugs for ≥12 weeks (≥16 weeks for pioglitazone) prior to randomization, and, for insulin, the dose was not to have been changed within 12 weeks prior to randomization by >10 % from the dose at randomization]. Exclusion criteria included the presence of significant comorbidities, including cardiovascular disease and renal impairment (i.e. an eGFR of <60 mL/min/1.73 m^2). The coprimary endpoints were the mean change from baseline to week 12 in HbA_{1c} level and mean 24-h SBP, with analyses conducted in the full analysis set. Background therapy with antihypertensive and antidiabetes drugs at an unchanged dose and regimen (if possible) was continued throughout the trial [49].

Once-daily empagliflozin 10 or 25 mg ($n = 276$/group) for 12 weeks provided significant and clinically relevant improvements in HbA_{1c} levels and 24-h SBP compared with placebo ($n = 271$) [49]. At 12 weeks, adjusted mean changes from baseline in HbA_{1c} in the empagliflozin 10 mg, empagliflozin 25 mg and placebo groups were −0.59, −0.62 and +0.03 %, respectively (both $p < 0.001$ vs. placebo; mean baseline HbA_{1c} 7.9 % in all groups). In the empagliflozin 10 and 25 mg group, adjusted mean reductions in mean 24-h SBP from baseline were 2.95 and 3.68 mmHg compared with an increase of 0.48 mmHg in the placebo group (both $p < 0.001$; mean baseline 24-h SBP 131.2–131.7 mmHg). Empagliflozin recipients also experienced significantly greater improvements from baseline in adjusted mean 24-h DBP and mean seated office SBP and DBP than placebo recipients at study end (all $p < 0.001$ for both empagliflozin groups vs. placebo) [49].

4.5.2 Patients with Renal Impairment

A 52-week, double-blind, multinational phase III trial evaluated the efficacy of add-on empagliflozin in patients with inadequately controlled type 2 diabetes (i.e. an HbA_{1c} level of 7–10 %) and stage 2 CKD (eGFR ≥60 to 90 mL/min/1.73 m^2; $n = 290$) or stage 3 CKD (eGFR ≥30 to <60 mL/min/1.73 m^2; $n = 374$) [50]. Major exclusion criteria included uncontrolled hyperglycaemia (i.e. glucose level of >13.3 mmol/L after an overnight fast), significant comorbidities (other than CKD), renal transplant, an eGFR of <15 mL/min/1.73 m^2 and requirement for chronic or acute dialysis. Patients were stratified by renal impairment, HbA_{1c} level and background antihyperglycaemic treatment prior to randomization to add-on empagliflozin or placebo; patients with stage 2 CKD received empagliflozin 10 or 25 mg once daily or placebo and stage 3 CKD patients received empagliflozin 25 mg once daily or placebo. For the first 24 weeks, patients continued their background antihyperglycaemic medication without change; thereafter, it could be changed at the investigator's discretion. A group of patients with type 2 diabetes and stage 4 CKD (i.e. an eGFR ≥15 to <30 mL/min/1.73 m^2; $n = 74$) were randomized to once-daily empagliflozin 25 mg or placebo; exploratory descriptive analyses for this group are tabulated (Table 4) [50].

Patients with stage 2 or 3 CKD receiving add-on empagliflozin therapy experienced significantly greater improvements in glycaemic control than those receiving add-on placebo, as assessed by adjusted mean changes in HbA_{1c} levels at 24 weeks (primary endpoint) and 52 weeks, and adjusted mean changes in FPG levels at these time points (Table 4) [50]. Significantly more patients with stage 2 CKD receiving add-on empagliflozin 25 mg than add-on placebo achieved a target HbA_{1c} level of <7 %, although there was no significant difference between the empagliflozin 10 mg and placebo group in this patient population or between the empagliflozin and placebo group in those with stage 3 CKD (Table 4). In patients with stage 2 or 3 CKD, add-on empagliflozin was associated with significantly greater reductions in bodyweight at week 24 and 52 than add-on placebo. In general, SBP was also reduced to a significantly greater extent at week 24 and 52 in the empagliflozin groups than in the respective placebo groups (Table 4).

5 Tolerability

Empagliflozin was generally well tolerated in clinical trials and extension studies discussed in Sect. 4. In a pooled analysis of five placebo-controlled trials of 18–24 weeks' duration, the overall incidence of adverse events in patients receiving empagliflozin ($n = 1,976$) was similar to that with placebo ($n = 995$) [18]. The most common (incidence ≥5 % in any treatment group) treatment-emergent adverse events occurring with empagliflozin monotherapy in a large, multinational, phase III trial are presented in Fig. 2 [39]. In this study, <1 % of patients in any treatment group experienced confirmed hypoglycaemic events (i.e. plasma glucose level of <3.9 mmol/L and/or requiring assistance) and no patients required assistance for hypoglycaemic events.

The frequency of minor and major (i.e. hypoglycaemia requiring assistance) hypoglycaemia with empagliflozin monotherapy or empagliflozin add-on therapy to metformin or pioglitazone with or without metformin was similar to that observed in placebo recipients [18]. When empagliflozin was used with a sulfonylurea or insulin, hypoglycaemia was the most frequently reported adverse reaction, with frequency of hypoglycaemia dependent on the background therapy. An increase in the frequency of minor hypoglycaemia was reported when empagliflozin was given as add-on therapy to metformin plus a sulfonylurea (add-on empagliflozin 10 mg/day 16.1 %, add-on empagliflozin 25 mg/day 11.5 % and add-on placebo 8.4 %) or as add-on therapy to insulin with or without metformin and with or without a sulfonylurea, both in the initial 18-week period when the insulin dose could not be adjusted (19.5, 27.1 and 20.6 %, respectively) and over the 78-week trial (36.1, 34.8 and 35.3 %, respectively). The frequency of major hypoglycaemia also increased when empagliflozin was given as add-on therapy to insulin with or without metformin and with or without a sulfonylurea, both in the initial 18-week period when the insulin dose could not be adjusted (add-on empagliflozin 10 mg/day 0 %, add-on empagliflozin 25 mg/day 1.3 % and add-on placebo 0 %) and over the 78-week trial (0, 1.3 and 0 %, respectively) [18]. In a 104-week phase III trial (see Table 3 for further design details), significantly fewer empagliflozin than glimepiride recipients (as add-on therapy to metformin) experienced confirmed hypoglycaemic adverse events by study end (2 vs. 24 %; adjusted relative risk 0.102; 95 % CI 0.065–0.162; $p < 0.001$) [43].

Common (occurring in 1–10 % of patients) adverse reactions reported in placebo-controlled trials were genital infections (including vaginal moniliasis, vulvovaginitis, balanitis), urinary tract infections (UTIs), pruritus (generalized) and increased urination [18]. Genital infections occurred more frequently in empagliflozin-treated patients than placebo recipients (empagliflozin 10 mg/day 4.1 %, empagliflozin 25 mg/day 3.7 vs. 0.9 % in placebo recipients), which was particularly apparent in female patients. These infections were of mild to moderate intensity. Increased urination was observed at a higher frequency in empagliflozin than in placebo recipients (3.4 % with

Table 4 Efficacy of add-on oral empagliflozin in adult patients with inadequately controlled type 2 diabetes mellitus and chronic kidney disease in a double-blind, multinational trial [50]. Results at the primary timepoint for the primary efficacy endpoint (i.e. 24 weeks) and at study end in the full analysis set

Endpoint (week)	Timepoint (weeks)	Stage 2 CKD (*n*)			Stage 3 CKD (*n*)		Stage 4 CKD[a] (*n*)	
		EMP 10[b] (94–98)	EMP 25[b] (91–97)	PL[b] (89–95)	EMP 25[b] (175–187)	PL[b] (178–187)	EMP 25[b] (37)	PL[b] (37)
Mean HbA_{1c} level (%)	Baseline	8.02	7.96	8.09	8.02	8.09	8.06	8.16
	AMC 24	−0.46****[c]	−0.63****[c]	+0.06[c]	−0.37****[c]	+0.05[c]	+0.04	−0.18
	AMC 52	−0.57****	−0.60****	+0.06	−0.32****	+0.12	+0.11	−0.37
% pts achieving HbA_{1c} of <7 %	24	17.0 (OR 2.65)	24.2 (OR 4.46**)	6.7	12.0 (OR 1.82)	7.9	NR	NR
Mean FPG (mmol/L)	Baseline	8.1	8.2	8.0	7.9	8.0	8.7	8.2
	AMC 24	−0.77****	−1.00****	+0.31	−0.5****	+0.6	−0.2	+0.6
	AMC 52	−1.15****	−0.80****	+0.41	−0.4**	+0.3	−0.3	+0.4
Mean bodyweight (kg)	Baseline	92.1	88.1	86.0	83.2	82.5	77.9	84.1
	AMC 24	−1.76****	−2.33****	−0.33	−0.98***	−0.08	−1.4	−0.1
	AMC 52	−2.00***	−2.60****	−0.44	−1.17****	0	−1.0	0
Mean SBP (mmHg)	Baseline	137.4	133.7	134.7	137.4	134.7	145.0	146.2
	AMC 24	−2.9*	−4.5**	+0.7	−3.9**	+0.4	−7.4	+1.2
	AMC 52	−1.7	−6.2****	+1.6	−5.1**	−0.8	−11.2	+1.0

AMC adjusted mean change, CKD chronic kidney disease, *EMP* empagliflozin, *FPG* fasting plasma glucose, *HbA_{1c}* glycated haemoglobin, *NR* not reported, *OADs* oral antidiabetic drugs, *OR* odds ratio (vs. PL), *PL* placebo, *pts* patients, *SBP* systolic blood pressure

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$, **** $p < 0.0001$ vs. PL for the given CKD population

[a] Descriptive analyses; data are all means

[b] Mg once daily; all pts continued their background therapy (OADs and/or insulin) unchanged for 24 weeks; thereafter, it could be adjusted at the investigator's discretion

[c] Primary endpoint

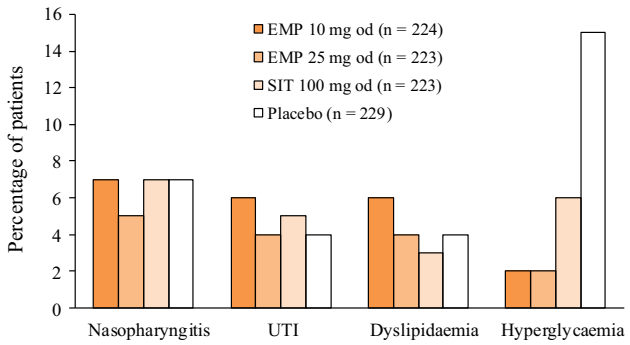

Fig. 2 Most common treatment-emergent adverse events occurring with oral empagliflozin or sitagliptin in a 24-week, multinational trial in adult patients with type 2 diabetes mellitus [39]. *EMP* empagliflozin, *od* once daily, *SIT* sitagliptin, *UTI* urinary tract infection

empagliflozin 10 mg/day and 3.2 % with empagliflozin 25 mg/day vs. 1.0 %) and was mostly of mild to moderate intensity. The frequency of nocturia was similar with empagliflozin to that with placebo. In the overall population, UTIs occurred more frequently with empagliflozin 10 mg/day than with placebo (9.3 vs. 7.6 %), but at a similar frequency to placebo with empagliflozin 25 mg/day. These infections occurred more frequently in patients with a history of chronic or recurrent UTIs for all groups and were of a similar intensity in all groups. UTIs occurred more frequently in female patients, but not male patients, treated with empagliflozin than in patients receiving placebo [18]. In another pooled analysis of 2,477 patients who participated in clinical trials, empagliflozin 10 or 25 mg once daily, as monotherapy or add-on therapy (to metformin ± a sulfonylurea or pioglitazone ± metformin) was not associated with an overall increased frequency of UTIs compared with placebo (8–9% in both groups), but was associated with an overall increased frequency of genital infections (4 vs. 1% in placebo recipients; abstract presentation) [52]. Most UTIs and genital infections were mild in intensity and most patients only experienced one episode, with genital infections occurring more commonly in women than men [52].

In a 52-week phase III trial in patients with type 2 diabetes and CKD (see Sect. 4.5.2 for further design details), the proportion of patients experiencing at least one investigator-defined drug-related adverse event was generally similar in the add-on empagliflozin 10 or 25 mg/day groups to that in the add-on placebo group (27.0–41.2 vs. 24.1–32.6 %) [50]. Most of these adverse events were of mild to moderate intensity. Conformed hypoglycaemia (i.e. plasma glucose level ≤3.9 mmol/L and/or requiring assistance) occurred in 22.7–37.8% of patients in the empagliflozin groups and 24.2–32.4 % of patients in the placebo groups, with <3 % of patients in any given group requiring assistance with these episodes. Small reductions in eGFR were observed in patients with stage 2, 3 or 4 CKD receiving empagliflozin; eGFR returned to baseline values by the end of the 3-week follow-up after completion of treatment. Patients with stage 2 or 3 CKD receiving empagliflozin 25 mg once daily experienced significant ($p < 0.05$) improvements in urine albumin to creatinine ratios compared with placebo recipients at week 52. In patients with stage 3 CKD, numerically fewer patients experienced a worsening of albuminuria, with 12.2 % of empagliflozin 25 mg/day recipients and 22.2 % of placebo recipients going from no albuminuria at baseline to microalbuminuria at study end, and 2 and 11.4 %, respectively, going from microalbuminuria at baseline to macroalbuminuria at study end. Moreover, numerically more empagliflozin than placebo recipients experienced an improvement in albuminuria, with 32.6 and 8.6 % of patients, respectively, going from macroalbuminuria at baseline to microalbuminuria at study end, and 27.5 and 21.4 % going from microalbuminuria at baseline to no albuminuria at study end [50].

6 Dosage and Administration

In the EU [18] and USA [53], oral empagliflozin is recommended for the treatment of adult patients with type 2 diabetes to improve glycaemic control. In the USA, it is recommended as an adjunct to diet and exercise [53]. In the EU, empagliflozin may be used as monotherapy in patients with inadequate glycaemic control despite diet and exercise alone and in whom metformin is considered inappropriate due to intolerance [18]. Empagliflozin may be used as add-on therapy in combination with other antihyperglycaemic agents, when these, together with diet and exercise, do not provide adequate glycaemic control [18, 53].

The recommended starting dosage is 10 mg once daily [53] as monotherapy or in combination with other antihyperglycaemic agents, including insulin [18]. In patients tolerating this dosage (who have an eGFR of ≥60 mL/min/1.73 m^2 and who require tighter glycaemic control [18]), the dosage of empagliflozin may be increased to 25 mg once daily (i.e. maximum dosage) [18, 53].

Empagliflozin should not be initiated in patients with an eGFR of <45 [53] or <60 mL/min/1.73 m^2 [18] or a creatinine clearance (CL_{CR}) of <60 mL/min [18]. In the EU [18], in patients with an eGFR of <60 mL/min/1.73 m^2 or a CL_{CR} of <60 mL/min who are tolerating empagliflozin, the dosage should be adjusted to or maintained at 10 mg once daily, with empagliflozin discontinued when the eGFR is persistently <45 mL/min/1.73 m^2. Empagliflozin is not expected to be effective in patients with ESRD or patients on haemodialysis and should not be used in these patient populations [18, 53]. Renal function should be

evaluated prior to initiating empagliflozin treatment and periodically monitored thereafter (at least yearly [18]) [53], with more frequent monitoring in elderly patients [53] and those with renal impairment [18, 53].

Empagliflozin may add to the diuretic effects of thiazide and loop diuretics and may increase the risk of dehydration and hypotension [18, 53]. A lower dose of insulin or an insulin secretagogue (e.g. sulfonylurea) may be required to reduce the risk of hypoglycaemia when these agents are used in combination with empagliflozin (see Sect. 5) [18, 53].

Local prescribing information should be consulted for detailed information regarding the use of empagliflozin in specific patient populations, contraindications, warnings and precautions.

7 Place of Empagliflozin in the Management of Type 2 Diabetes Mellitus

The progressive nature of type 2 diabetes means that although management initially focuses on lifestyle changes, it invariably necessitates pharmacological intervention, with pharmacotherapy (typically with metformin monotherapy or combination therapy depending upon HbA_{1c} levels) initiated at the time of or soon after diagnosis of the disease [2, 6, 54]. To minimize the risks of diabetes-related complications, current guidelines for the management of type 2 diabetes recommend that a target HbA_{1c} level of <7 % (for most patients) is achieved and maintained, although in certain individuals glycaemic levels higher or lower than this target may be appropriate. To achieve this level of glycaemic control, the majority of patients require combination therapy with at least two antihyperglycaemic drugs that have complementary modes of action. Treatment should be initiated as early in the course of the disease as possible and, given the heterogeneity in the pathogenesis of the disease, should be individualized based on the clinical manifestations of the disease, existing comorbidities and responses to individual antihyperglycaemic pharmacotherapy (both efficacy and safety) [2, 6, 54]. Indeed, evidence indicates that initiating treatment during the early stages of diabetes has a more marked impact on cardiovascular outcomes than that observed when treatment is initiated in the latter stages after a prolonged period of hyperglycaemia [55, 56].

Optimization of treatment for individual patients has been facilitated by the increasing availability of various classes of antihyperglycaemic drugs that have differing but complementary mechanisms of action and/or differing safety profiles, propensities for drug-drug interactions and routes of administration [2, 6, 54]. Based on the most recent guidelines [54], SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin), of which empagliflozin is the most recent one to be approved in the EU and USA, may be used as first-line monotherapy (though not typically as a first choice) or add-on therapy to other antihyperglycaemic agents, including insulin, as dual or triple combination therapy. The introduction of SGLT2 inhibitors generally occurred after publication of most current guidelines. In the clinical practice setting, it seems most likely that the main role of empagliflozin, as with other SGLT2 inhibitors, will be as add-on therapy to other antihyperglycaemic drugs, as stated recently by the UK National Institute for Health and Care Excellence [57] and indicated in recent treatment algorithms [54]. SGLT2 inhibition provides a unique insulin-independent, complementary mechanism of action when used in combination regimens, whereby inhibition of SGLT2 reduces reabsorption of filtered glucose in the proximal tubules of the kidneys and lowers the renal threshold for glucose, thereby increasing UGE and reducing blood glucose levels (see Sect. 2). By contrast, the majority of currently available OADs act, at least in part, in an insulin-dependent manner to reduce hyperglycaemia by stimulating insulin secretion or improving insulin sensitivity in target tissues [7, 8].

Ideally, antihyperglycaemic agents should target not only glycaemic control, but also aim to minimize the risk of adverse outcomes such as bodyweight gain and hypoglycaemia, both of which are considered cardiovascular risk factors [6]. Most patients with type 2 diabetes are overweight or obese, with obesity per se associated with insulin resistance [1]. The various classes of antihyperglycaemics have differing impacts on bodyweight, with SGLT2 inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists (e.g. exenatide) and amylin agonists (e.g. pramlinitide) associated with bodyweight loss, whilst biguanides (e.g. metformin), DPP-4 inhibitors (e.g. sitagliptin) and α-glucosidase inhibitors (e.g. acarbose) are bodyweight neutral and sulfonylureas (e.g. glimepiride), thiazolidinediones (e.g. pioglitazone), meglitinides (e.g. repaglinide) and insulin are associated with bodyweight gain [2, 6]. SGLT-2 inhibitors, biguanides, thiazolidinediones, GLP-1 receptor agonists and DPP-4 inhibitors have no intrinsic risk for increasing the incidence of hypoglycaemia, albeit with some of these agents such as SGLT2 inhibitors and GLP-1 receptor agonists, the risk of hypoglycaemia increases when coadministered with a sulfonylurea and/or insulin. Both of these latter classes of antihyperglycaemics are associated with episodes of hypoglycaemia, some of which may necessitate hospitalization or cause death, with hypoglycaemia a key limiting factor in the management of type 2 diabetes [2, 6].

In large clinical trials (≤104 weeks' duration; typically 24 weeks) discussed in Sect. 4, including Japanese studies, empagliflozin 10 or 25 mg once daily as monotherapy

(Sect. 4.1) or add-on therapy to metformin (Sect. 4.2) and/or to other OADs (Sect. 4.3) or insulin (Sect. 4.4) significantly improved glycaemic control, bodyweight and SBP compared with placebo monotherapy or add-on therapy. As add-on therapy to metformin, empagliflozin was shown to be noninferior to glimepiride at 52 weeks and superior to glimepiride at 104 weeks, in terms of reductions in HbA_{1c} levels, with adjusted mean changes in FPG, bodyweight and SBP also significantly greater in the empagliflozin group than in the glimepiride group (Sect. 4.2). Add-on empagliflozin treatment also significantly improved glycaemic control and, where evaluated, SBP and/or DBP and bodyweight in patients with type 2 diabetes and hypertension (Sect. 4.5.1) or stage 2 or 3 CKD (4.5.2). Improvements in glycaemic control with empagliflozin monotherapy (Sect. 4.1) or add-on therapy (Sect. 4.2) were maintained after up to 104 weeks' treatment. The relative position of empagliflozin compared with most other antihyperglycaemics remains to be determined, with a lack of head-to-head trials comparing empagliflozin with most OADs, including other SGLT2 inhibitors and DPP-4 inhibitors, and with subcutaneous GLP-1 receptor agonists.

The high prevalence of cardiovascular disease in patients with type 2 diabetes means that establishing the impact of antihyperglycaemic agents on long-term clinical cardiovascular outcomes is important. Currently, data from long-term trials evaluating the impact of empagliflozin treatment on these outcomes are lacking. An ongoing, multinational, empagliflozin cardiovascular outcome event trial in patients with type 2 diabetes who have an elevated cardiovascular risk ($n = 7{,}042$ randomized) will assess the impact of recommended dosages of empagliflozin compared with placebo on cardiovascular events, with the primary endpoint being the time-to-first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke [58].

Empagliflozin was well tolerated in adult patients with type 2 diabetes participating in clinical trials of up to 104 weeks' duration (Sect. 5). Most treatment-emergent adverse events were of mild to moderate intensity, with relatively few patients discontinuing treatment because of an adverse event. Empagliflozin therapy appeared to have no intrinsic risk of hypoglycaemia (as monotherapy or add-on therapy to metformin and/or pioglitazone, hypoglycaemia occurred with a similar frequency as that with placebo), although the frequency of these episodes was dependent upon the background antihyperglycaemic therapy (Sect. 5). Hence, to reduce the risk of hypoglycaemia, a reduction in the dose of insulin or insulin secretagogues may be required if these agents are used in combination with empagliflozin (Sect. 6). Genital infections, most of which were mild or moderate in intensity, appeared to occur more frequently in empagliflozin-treated patients than in placebo recipients (potentially related to the mechanism of action of SGLT2 inhibitors), especially in female patients (Sect. 5).

Albeit that no causal link has been established, concerns have been raised regarding a potential increased risk for bladder and breast cancer with SGLT-2 inhibitor treatment, based on an increased risk of breast and bladder cancer occurring during clinical trials of dapagliflozin [59–62]. Canagliflozin has not demonstrated an increased risk of breast and bladder cancer in placebo-controlled trials [62]. In clinical trials, the overall number of empagliflozin-treated patients who developed kidney or bladder cancer was low and similar to that in placebo recipients; no obvious mechanism has been identified whereby empagliflozin could increase the risk of renal cancer [63]. A post-marketing surveillance study to assess the risk of renal and bladder cancer in empagliflozin-treated patients compared with patients treated with other diabetic agents was proposed by the European Medicines Agency as part of the post-authorization development plan [63]. Long-term clinical experience should help to define the benefit-risk ratio of SGLT-2 inhibitor treatment.

Globally, type 2 diabetes is associated with significant costs from a societal and healthpayer perspective, with these costs being an important consideration in determining the choice of treatment. Given the recent approval of empagliflozin, it is not unexpected that robust pharmacoeconomic data are lacking.

In conclusion, oral once-daily empagliflozin monotherapy or add-on therapy to other antihyperglycaemics, including insulin, was an effective and well tolerated treatment in adult patients with type 2 diabetes. With its insulin-independent mechanism of action and convenient administration regimen, empagliflozin monotherapy or combination therapy with other antidiabetic drugs, including insulin, provides a useful addition to the therapeutic options for the management of type 2 diabetes.

Data selection sources: Relevant medical literature (including published and unpublished data) on empagliflozin was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 15 September 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Empagliflozin, type 2 diabetes mellitus, diabetes mellitus, non-insulin dependent diabetes mellitus, T2DM.
Study selection: Studies in patients with type 2 diabetes mellitus who received empagliflozin. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Disclosure The preparation of this review was not supported by any external funding. Lesley Scott is a salaried employee of Adis/Springer. During the peer review process, the manufacturer of the

agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the authors on the basis of scientific and editorial merit.

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