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ADIS DRUG EVALUATION

Empagliflozin/Linagliptin: A Review in Type 2 Diabetes

Esther S. Kim[1] · **Emma D. Deeks**[1]

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Abstract Empagliflozin/linagliptin (Glyxambi®) is a once-daily sodium glucose co-transporter type 2 (SGLT2) inhibitor and dipeptidyl peptidase (DPP)-4 inhibitor fixed-dose combination product that is approved in the USA as an adjunct to diet and exercise in adults with type 2 diabetes (T2D) when treatment with both empagliflozin and linagliptin is appropriate. This article reviews the clinical efficacy and tolerability of oral empagliflozin/linagliptin in patients with T2D and summarizes the pharmacological properties of the agents. Results of two randomized controlled trials of 52 weeks' duration in adults with T2D demonstrated that empagliflozin/linagliptin improved glycaemic control significantly more than linagliptin when administered as initial therapy (whereas results vs. empagliflozin were mixed in this setting) and significantly more than linagliptin or empagliflozin when administered as an add-on therapy to metformin. In addition to glycaemic control, empagliflozin/linagliptin provided significant weight loss compared with linagliptin in both trials. Empagliflozin/linagliptin was generally well tolerated in patients with T2D, with a low risk of hypoglycaemia and no reports of exacerbations of, or hospitalizations for, heart failure during the trials. As the first SGLT2 inhibitor/DPP-4 inhibitor fixed-dose combination available, empagliflozin/linagliptin is a useful new option for patients with T2D.

Empagliflozin/Linagliptin in type 2 diabetes: a summary

Fixed-dose combination of a sodium glucose co-transporter type 2 inhibitor and a dipeptidyl peptidase-4 inhibitor with convenient once-daily oral administration
Generally improves glycaemic control more than its individual components, when used as an initial therapy or as an add-on to metformin, although findings vs. empagliflozin were mixed in the initial therapy setting
Also significantly improves bodyweight compared with linagliptin
Generally well tolerated, with a low risk of hypoglycaemia

The manuscript was reviewed by: ***M. Abdul-Ghani***, University of Texas Health and Science Center at San Antonio, Diabetes Division, San Antonio, TX, USA; ***D. S. H. Bell***, Southside Endocrinology, University of Alabama Medical School, Birmingham, AL, USA; ***A. J. Scheen***, University of Liège, Division of Diabetes, Nutrition and Metabolic Disorders and Clinical Pharmacology Unit, Liège, Belgium.

✉ Esther S. Kim
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand

1 Introduction

Over 29 million Americans have diabetes mellitus, and type 2 diabetes (T2D) accounts for ≈90–95 % of cases in adults [1]. Although more than nine different classes of oral pharmacological agents and a variety of insulin and non-insulin injection products are available for the treatment of T2D, ≈50 % of patients still fail to meet recommended goals for diabetes care [2, 3].

Metformin is the drug of choice for monotherapy in patients with T2D based on efficacy, safety, weight neutrality, low cost and the possibility of cardiovascular benefits [4, 5]. However, some patients may need to start monotherapy with a second-line agent [e.g. dipeptidyl peptidase (DPP)-4 inhibitor, glucagon-like peptide (GLP)-1 receptor agonist, basal insulin, sodium glucose co-transporter type 2 (SGLT2) inhibitor, sulfonylurea or thiazolidinedione] when metformin is contraindicated or not tolerated. Many patients eventually move on to combination therapy (dual or triple) because of the progressive nature of the disease, and initial dual-combination therapy should be considered in patients with glycated haemoglobin (HbA_{1c}) ≥9 %, to expedite glycaemic control [4, 5]. Each new class of a noninsulin antidiabetic drug added to initial therapy is thought to lower HbA_{1c} by ≈1 % [5, 6].

SGLT2 inhibitors and DPP-4 inhibitors are two classes of glucose-lowering drugs that have been developed for the treatment of T2D in the last decade [7]. SGLT2 inhibitors (e.g. canagliflozin, dapagliflozin, empagliflozin) prevent renal glucose reabsorption and promote urinary glucose excretion [8]. DPP-4 inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) prevent the degradation of endogenous incretin hormones and enhance glucose-dependent insulin secretion and glucagon suppression [9]. Empagliflozin/linagliptin (Glyxambi®) is the first fixed-dose combination of an SGLT2 inhibitor and DPP-4 inhibitor that has been approved in the USA as an adjunct to diet and exercise for adults with T2D to improve glycaemic control [10]. This article summarizes pharmacological, efficacy and tolerability data relevant to the use of empagliflozin/linagliptin in this indication. The individual drugs were reviewed in *Drugs* previously [11, 12].

2 Pharmacodynamic Properties of Empagliflozin and Linagliptin

Empagliflozin and linagliptin have complementary mechanisms of action [10]. Empagliflozin inhibits SGLT2, the predominant transporter involved in reabsorbing ≈90 % of glucose from the glomerular filtrate back into the circulation, and thereby increases urinary glucose excretion, which lowers blood glucose levels [10, 13]. Linagliptin inhibits DPP-4, an enzyme that rapidly degrades glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 (both incretin hormones), and thereby stimulates insulin release and decreases circulating glucagon levels in a glucose-dependent manner [10, 14].

Both empagliflozin and linagliptin are potent and highly selective in their inhibition of SGLT2 and DPP-4 [15, 16]. In vitro studies indicated that the empagliflozin concentration at half-maximal inhibition (IC_{50}) was 3.1 nmol/L for SGLT2 versus 1100–11,000 nmol/L for other SGLTs [16], and that the IC_{50} of linagliptin was 1 nmol/L for DPP-4 versus 89 to >100,000 nmol/L for other peptidases and proteases [15]. Empagliflozin was >350- to >3500-fold more selective for SGLT2 over other SGLTs (e.g. >2500-fold more selective for SGLT2 over SGLT1) [16], and linagliptin was >10,000- to 100,000-fold more selective for DPP-4 over other evaluated DPPs (e.g. 40,000- and >10,000-fold more selective for DPP-4 over DPP-8 and -9, respectively) [15].

Empagliflozin inhibited the reabsorption of glucose and induced glucosuria in healthy volunteers [17, 18] and patients with T2D [19–22], including in the fed and fasted states [22]. For example, the administration of oral empagliflozin 10, 25 or 100 mg once daily in patients with T2D inhibited filtered glucose reabsorption by 36, 42 and 45 %, respectively, and consequently, significantly ($p < 0.0001$) increased urinary glucose excretion by ≈11-, 18- and 14-fold, respectively, from baseline to day 1 compared with placebo, and these effects were maintained at day 27 [20]. In addition, empagliflozin reduced fasting plasma glucose (FPG) [19–22] and mean daily plasma glucose (MDG) levels [19, 20], as well as HbA_{1c} levels [20–22], in patients with T2D, although some changes were not significant versus placebo with some of the dosages assessed (patients received empagliflozin 1–100 mg/day in these trials) [19–22]. For example, the administration of oral empagliflozin 10–100 mg once daily in patients with T2D resulted in significant ($p < 0.05$) reductions from baseline to day 28 in mean FPG (all doses) and from baseline to day 27 in MDG (empagliflozin 25 and 100 mg) compared with placebo [20]. The change from baseline to day 28 in HbA_{1c}, although not significant, was −0.22 to −0.36 % with empagliflozin versus −0.18 % with placebo [20].

Increases in intact GIP [23] and GLP-1 [23–25] were seen with linagliptin at some dosages in patients with T2D (1–10 mg/day was assessed). For example, the placebo-corrected area under the time-effect curve between 0 and 2 h ($AUEC_{0–2\ h}$) for intact GIP increased from baseline by ≈1.5-fold on day 1 ($p = 0.003$) and twofold on day 28 ($p < 0.0001$) in patients with T2D receiving oral linagliptin 5 mg once daily, and increases of a similar magnitude were seen with linagliptin for intact GLP-1 on day 1 ($p < 0.0001$) and day 28 ($p < 0.0001$) [23]. In addition, linagliptin reduced FPG and HbA_{1c} levels in patients with T2D [23, 25]. Linagliptin also reduced glucagon levels [23]. For example, in the trial of patients receiving oral linagliptin 5 mg or placebo once daily [23], linagliptin resulted in significant mean reductions from baseline to day 28 compared with placebo for glucagon $AUEC_{0–2\ h}$ (−17.4 vs. 1.3 pg·h/mL; $p = 0.045$), FPG (−10.8 vs. −0.18 mg/dL; $p = 0.028$) and HbA_{1c} (−0.27 vs. −0.06 %; $p = 0.002$) [23].

In healthy volunteers, neither empagliflozin (25 or 200 mg) nor linagliptin (5 or 100 mg) was associated with clinically relevant changes in the heart-rate corrected QT interval [26, 27].

3 Pharmacokinetic Properties of Empagliflozin and Linagliptin

This section focuses on the pharmacokinetics of empagliflozin and linagliptin as individual agents, as data for fixed-dose empagliflozin/linagliptin are currently limited. However, bioequivalence has been established for the 25/5 mg fixed-dose tablet and the individual drugs coadministered at corresponding doses [10].

3.1 Absorption and Distribution

Empagliflozin and linagliptin are both rapidly absorbed after oral administration [20, 24]. In patients with T2D, empagliflozin 10–100 mg and linagliptin 1–10 mg (administered as separate drugs in separate trials) had a median time to steady-state maximum plasma concentration of ≈1.5 h following oral administration, both after single and multiple dosing. Systemic exposure increased dose-proportionally for empagliflozin and dose-dependently but less than dose-proportionally for linagliptin [20, 24]. In healthy male volunteers administered empagliflozin 50 mg with linagliptin 5 mg, the total exposure of each drug was unaffected by the other, the peak exposure of linagliptin was unaffected by empagliflozin, and although the peak exposure of empagliflozin decreased by ≈12 % when administered with linagliptin, this reduction was not considered clinically significant [28].

The apparent volume of distribution at steady state is ≈73.8 L for empagliflozin and ≈1110 L (indicating extensive distribution into the tissues) for linagliptin [10]. Plasma concentrations decline in a biphasic manner for empagliflozin, with a rapid distribution phase and a slower terminal phase, and in at least a biphasic manner for linagliptin [19, 29]. Unlike empagliflozin, which exhibits linear pharmacokinetics, linagliptin has nonlinear pharmacokinetics because of its high-affinity binding to DPP-4 in tissues and plasma [20, 30]. In healthy subjects administered oral ^{14}C-labeled empagliflozin, plasma protein binding was 86.2 % [10]. Plasma protein binding was concentration-dependent for linagliptin and reflected a saturation of DPP-4 binding at higher concentrations, with protein binding of 99 % at 1 nmol/L and 75–89 % at ≥30 nmol/L [10]. The effect of high-fat meals on empagliflozin [17, 31] and linagliptin [30] was not considered to be clinically relevant; empagliflozin/linagliptin may be administered with or without food [10].

3.2 Metabolism and Elimination

Glucuronidation by the uridine 5′-diphospho-glucuronosyltransferases (UGT) 1A3, 1A8, 1A9 and 2B7 has been suggested as the primary route of metabolism for empagliflozin, based on in vitro studies [10]. No major metabolites were detected in human plasma for empagliflozin, and systemic exposure to glucuronide conjugates accounted for <10 % of drug-related material. In healthy subjects, ≈95.6 % of ^{14}C-labeled empagliflozin was eliminated in urine (54.4 %, approximately half of which was unchanged parent drug) and faeces (41.2 %, of which the majority was unchanged parent drug). Empagliflozin had an apparent terminal elimination half-life of ≈12.4 h and an apparent oral clearance of 10.6 L/h [10].

Metabolism is a minor elimination pathway for linagliptin [32]. In healthy subjects, ≈90 % of ^{14}C-labeled linagliptin 10 mg was excreted unchanged in urine and faeces following oral administration, with the majority (≈85 %) eliminated via faeces. A small fraction of the drug was observed in the plasma as CD1790, an inactive metabolite of linagliptin, and it was the only metabolite that accounted for >10 % of total drug-related compounds following oral administration [32]. The renal clearance of linagliptin at steady state was ≈70 mL/min [10].

3.3 Special Patient Populations and Potential Drug Interactions

Renal function should be evaluated prior to and periodically during empagliflozin/linagliptin therapy because empagliflozin increases serum creatinine levels and decreases the estimated glomerular filtration rate (eGFR) [10]. Empagliflozin/linagliptin should not be started in patients with an eGFR of <45 mL/min/1.73 m^2 and is contraindicated in patients with severe renal impairment, end-stage renal disease or on dialysis [10]. Studies indicate that changes in exposure to empagliflozin or linagliptin in hepatically impaired subjects are not clinically relevant [33, 34]. Age, body size, gender and ethnic origin do not have a clinically relevant effect on empagliflozin or linagliptin pharmacokinetics [10].

Empagliflozin/linagliptin has a low potential for drug interactions. Empagliflozin and linagliptin do not induce or inhibit cytochrome P450 (CYP) isoforms, with the sole exception of weak to moderate inhibition of CYP3A4 by linagliptin [10]. Empagliflozin does not inhibit UGT1A1 and is not a substrate or inhibitor of organic anion transporter (OAT) 1 or organic cation transporter (OCT) 2. In addition, linagliptin has a low propensity for causing drug interactions with OCT substrates. Both empagliflozin and linagliptin are substrates for P-glycoprotein (P-gp), but both are unlikely to interact with other P-gp substrates at

therapeutic doses [10]. In vivo, rifampicin decreased the exposure of linagliptin, suggesting there may be a reduction of linagliptin efficacy when administered concomitantly with strong inducers of CYP3A4 or P-gp; an alternative to linagliptin is strongly recommended in patients requiring such drugs [10]. Empagliflozin is also a substrate for breast cancer resistance protein, OAT 3 and organic anion-transporting polypeptide 1B1 and 1B3, but it does not inhibit these transporters at therapeutic doses [10].

There were no clinically relevant pharmacokinetic drug-drug interactions when either empagliflozin or linagliptin was administered with drugs such as metformin, simvastatin or warfarin [10, 35]. However, insulin or insulin secretagogues (e.g. sulfonylureas), which are known to cause hypoglycaemia, were associated with a higher rate of hypoglycaemia in a clinical trial when used in combination with empagliflozin or linagliptin [10].

4 Therapeutic Efficacy of Empagliflozin/Linagliptin

The efficacy of oral empagliflozin/linagliptin, as initial combination therapy (Sect. 4.1) or as add-on therapy to metformin (Sect. 4.2), was investigated in two randomized, double-blind, parallel-group, multinational, phase III trials in adult patients with T2D [36, 37]. Enrolled patients were aged ≥18 years with HbA_{1c} levels >7 to ≤10.5 % despite a regimen of diet and exercise in both trials [36, 37] and metformin in the add-on trial [36].

The initial combination therapy trial [37] enrolled patients who had not received oral antidiabetic drugs (OADs), insulin or a GLP-1 analogue for ≥12 weeks prior to randomization (including drug-naïve patients), whereas the add-on trial [36] enrolled patients who had received only immediate-release metformin for ≥12 weeks at an unchanged dosage (≥1500 mg/day, maximum dosage according to the local label or a maximum tolerated dosage). Exclusion criteria included uncontrolled hyperglycaemia (i.e. a glucose level of >240 mg/dL following an overnight fast, confirmed by a second measurement during the placebo run-in period) and an eGFR of <60 mL/min/1.73 m^2 [36, 37]. Following a 2-week placebo run-in period, eligible patients were randomized to receive empagliflozin/linagliptin 10/5 mg, empagliflozin/linagliptin 25/5 mg, empagliflozin 10 mg, empagliflozin 25 mg or linagliptin 5 mg once daily every morning for 52 weeks [36, 37]. In the add-on trial, patients also received metformin at an unchanged dose for 52 weeks [36].

The primary efficacy endpoint in both trials was the change in HbA_{1c} from baseline to week 24 (assessed using an analysis of covariance model) [36, 37]. Efficacy analyses were performed in the full analysis set populations and compared empagliflozin/linagliptin (10/5 and 25/5 mg) with the respective individual components of empagliflozin (10 or 25 mg) and linagliptin (5 mg) [36, 37].

4.1 Initial Combination Therapy

As initial therapy, empagliflozin/linagliptin improved glycaemic control to a significantly greater extent than linagliptin, but results were mixed compared with empagliflozin [37]. Significantly greater reductions from baseline in HbA_{1c} were seen at week 24 with empagliflozin/linagliptin 10/5 mg compared with the individual components at the same dosages and with empagliflozin/linagliptin 25/5 mg versus linagliptin 5 mg, but not versus empagliflozin 25 mg (Table 1).

In patients with baseline HbA_{1c} ≥7 %, significantly ($p < 0.05$) more empagliflozin/linagliptin 10/5 and 25/5 mg recipients achieved HbA_{1c} <7 % at week 24 compared with recipients of the respective individual components (62.3 and 55.4 vs. 32.3–41.5 % of patients) [37]. In patients with baseline HbA_{1c} ≥8.5 % ($n = 34$–46 in each group), a significantly ($p < 0.05$) greater reduction in HbA_{1c} was seen at week 24 with empagliflozin/linagliptin 10/5 mg compared with the individual components and with empagliflozin/linagliptin 25/5 mg versus linagliptin 5 mg, but not versus empagliflozin 25 mg. In patients with baseline HbA_{1c} <8.5 %, empagliflozin/linagliptin 10/5 mg resulted in significantly ($p \leq 0.001$) greater reductions in HbA_{1c} compared with the individual components, but no significant differences were seen between empagliflozin/linagliptin 25/5 mg and the individual components at week 24 [37].

Results were also mixed for FPG levels and bodyweight [37]. Mean FPG levels and bodyweight were reduced to a significantly greater extent from baseline to week 24 with empagliflozin/linagliptin 10/5 mg versus linagliptin 5 mg but not versus empagliflozin 10 mg, and with empagliflozin/linagliptin 25/5 mg versus linagliptin 5 mg but not versus empagliflozin 25 mg (Table 1). The significant reductions in bodyweight seen with empagliflozin/linagliptin versus linagliptin only occurred in patients with baseline HbA_{1c} <8.5 % (abstract presentation) [38].

The reductions in HbA_{1c}, FPG and bodyweight achieved with empagliflozin/linagliptin 10/5 and 25/5 mg by week 24, including any significant benefits over the individual agents, were maintained up to week 52 of treatment (Table 1). Moreover, the proportion of patients with baseline HbA_{1c} ≥7 % achieving HbA_{1c} <7 % remained significantly ($p < 0.05$) greater at week 52 with empagliflozin/linagliptin 10/5 mg compared with the individual components and with empagliflozin/linagliptin 25/5 mg versus linagliptin 5 mg, but not versus empagliflozin

Table 1 Efficacy of oral fixed-dose empagliflozin/linagliptin relative to the respective individual components. Results from the initial combination [37] and second-line (add-on to metformin) [36] trials

Trial	Treatment (mg once daily)	No. of pts[a]	HbA_{1c} (%)			FPG (mg/dL)			Bodyweight (kg)		
			BL	Change to week 24[b]	Change to week 52	BL	Change to week 24	Change to week 52	BL	Change to week 24	Change to week 52
Initial combination											
Lewin et al. [37]	EMPA/LINA 10/5	135	8.04	−1.24**,‡‡‡	−1.22**,‡‡‡	157.2	−28.21‡‡‡	−23.8‡‡‡	87.3	−2.7‡‡‡	−1.6‡
	EMPA/LINA 25/5	134	7.99	−1.08‡‡‡	−1.17‡‡‡	156.1	−29.55‡‡‡	−25.3‡‡‡	87.9	−2.0‡	−2.0‡‡
	EMPA 10	132	8.05	−0.83	−0.85	160.3	−22.39	−16.8	87.8	−2.3	−2.3
	EMPA 25	133	7.99	−0.95	−1.01	152.8	−24.24	−19.9	86.7	−2.1	−2.4
	LINA 5	133	8.05	−0.67	−0.51	156.0	−5.92	2.8	89.5	−0.8	−0.3
Add-on to metformin											
DeFronzo et al. [36]	EMPA/LINA 10/5	135	7.95	−1.08**,‡‡‡	−1.05**,‡‡‡	156.7	−32.2*,‡‡‡	−24.7‡‡‡	86.6	−2.6‡‡‡	−2.7‡‡‡
	EMPA/LINA 25/5	134	7.90	−1.19†,‡‡‡	−1.21†,‡‡‡	154.6	−35.3†,‡‡‡	−33.1†,‡‡‡	85.5	−3.0‡‡‡	−3.1‡‡‡
	EMPA 10	137	8.00	−0.66	−0.69	161.6	−20.8	−16.9	85.7	−2.5	−2.9
	EMPA 25	140	8.02	−0.62	−0.64	159.9	−18.8	−12.7	87.7	−3.2	−2.8
	LINA 5	128	8.02	−0.70	−0.48	156.3	−13.1	−4.4	85.0	−0.7	−0.3

All values are means and all changes are adjusted values

BL baseline, *EMPA* empagliflozin, *FPG* fasting plasma glucose, HbA_{1c} glycated haemoglobin, *LINA* linagliptin, *pts* patients

* $p < 0.01$, ** $p < 0.001$ vs. EMPA 10 mg; † $p < 0.001$ vs. EMPA 25 mg; ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ vs. LINA 5 mg

[a] No. of pts in the full analysis set

[b] Primary endpoint

25 mg [37]. No significant differences from baseline to week 52 in diastolic blood pressure (DBP) or systolic blood pressure (SBP) were seen with empagliflozin/linagliptin 10/5 or 25/5 mg compared with the respective individual components [37].

4.2 Add-on Therapy to Metformin

As add-on therapy to metformin, empagliflozin/linagliptin improved glycaemic control to a significantly greater extent than empagliflozin or linagliptin alone [36]. Significantly greater reductions from baseline in HbA_{1c} were seen at week 24 with empagliflozin/linagliptin 10/5 and 25/5 mg compared with the individual components at corresponding dosages (Table 1).

In patients with baseline HbA_{1c} ≥7 %, significantly ($p < 0.001$) more empagliflozin/linagliptin 10/5 and 25/5 mg recipients achieved HbA_{1c} <7 % at week 24 compared with recipients of the respective individual components (57.8 and 61.8 % vs. 28.0–36.1 % of patients) [36]. In patients with HbA_{1c} ≥8.5 %, a significantly ($p \leq 0.001$) greater reduction in HbA_{1c} was seen at week 24 with empagliflozin/linagliptin 10/5 mg versus linagliptin 5 mg but not versus empagliflozin 10 mg, and with empagliflozin 25/5 mg compared with the individual components. In patients with baseline HbA_{1c} <8.5 %, empagliflozin/linagliptin 10/5 and 25/5 mg resulted in significantly ($p < 0.01$) greater reductions in HbA_{1c} compared with the respective individual components [36].

Mean FPG levels were reduced to a significantly greater extent from baseline to week 24 with empagliflozin/linagliptin 10/5 and 25/5 mg compared with the respective individual components (Table 1). Reductions from baseline in bodyweight were significantly greater with empagliflozin/linagliptin 10/5 mg versus linagliptin 5 mg but not versus empagliflozin 10 mg, and with empagliflozin 25/5 mg versus linagliptin 5 mg but not versus empagliflozin 25 mg at week 24 (Table 1). The significant reductions in bodyweight seen with empagliflozin/linagliptin versus linagliptin occurred both in patients with baseline HbA_{1c} ≥8.5 % and in patients with baseline HbA_{1c} <8.5 % (abstract presentation) [38].

Significant reductions in HbA_{1c}, FPG and bodyweight achieved by week 24 with empagliflozin/linagliptin 10/5 and 25/5 mg relative to the individual components were maintained up to week 52 of treatment (Table 1), with the exception of FPG in empagliflozin/linagliptin 10/5 mg recipients (which was no longer significantly reduced vs. empagliflozin 10 mg recipients) (Table 1). Moreover, as at week 24, significantly ($p < 0.05$) more patients with baseline HbA_{1c} ≥7 % achieved HbA_{1c} <7 % with empagliflozin/linagliptin 10/5 and 25/5 mg compared with the individual components at week 52 [36]. When mean changes from baseline in blood pressure were

assessed, at trial end, empagliflozin/linagliptin 10/5 or 25/5 mg had significantly reduced SBP ($p < 0.05$) but not DBP ($p = 0.05$) relative to linagliptin 5 mg; no significant differences in these parameters were seen between the 10/5 or 25/5 mg combinations and the corresponding empagliflozin component (10 or 25 mg) [36].

5 Tolerability and Safety of Empagliflozin/Linagliptin

5.1 General Tolerability Profile

Oral empagliflozin/linagliptin 10/5 or 25/5 mg once daily was generally well tolerated in patients with T2D, in the 52-week initial combination therapy [37] and add-on to metformin [36] trials. In a pooled analysis ($n = 1363$), adverse events occurred in 71.0 % of empagliflozin/linagliptin 10/5 mg recipients and 73.6 % of empagliflozin/linagliptin 25/5 mg recipients compared with 70.4–74.9 % of patients receiving the individual components at the same dosages (abstract presentation) [39], and the most common adverse events (incidence ≥5 %) with empagliflozin/linagliptin 10/5 or 25/5 mg were urinary tract infections (UTIs), upper respiratory tract infections and nasopharyngitis [10]. Most adverse events were mild to moderate in severity and deemed unrelated to the study drug [36, 37].

In the initial combination therapy trial, drug-related adverse events occurred in a proportion of empagliflozin/linagliptin 10/5 mg (10.3 %) and empagliflozin/linagliptin 25/5 mg (16.9 %) recipients as well as recipients of empagliflozin 10 mg (11.9 %), empagliflozin 25 mg (16.3 %) or linagliptin 5 mg (12.6 %) [37]. The most commonly occurring adverse events associated with empagliflozin/linagliptin initial combination therapy are presented in Fig. 1a. Serious adverse events occurred in 5.1 % of empagliflozin/linagliptin 10/5 mg recipients and 4.4 % of empagliflozin/linagliptin 25/5 mg recipients compared with 7.4 % of empagliflozin 10 mg recipients, 6.7 % of empagliflozin 25 mg recipients and 1.5 % of linagliptin 5 mg recipients. Adverse events led to treatment discontinuation in 5.9, 6.6, 5.2, 3.7 and 1.5 % of patients in the corresponding treatment groups [37].

In the trial that assessed empagliflozin/linagliptin as add-on therapy to metformin [36], the adverse event profile of empagliflozin/linagliptin was generally similar to that seen in the initial combination trial (Fig. 1) [37], with the exception of adverse events known to be associated with metformin, such as diarrhoea [5]. Drug-related adverse events were reported in 16.9 % of empagliflozin/linagliptin 10/5 mg recipients and 13.1 % of empagliflozin/linagliptin 25/5 mg recipients compared with 18.6 % of empagliflozin 10 mg recipients, 18.4 % of empagliflozin 25 mg recipients and 11.4 % of linagliptin 5 mg recipients [36]. The most commonly occurring adverse events associated with empagliflozin/linagliptin as add-on therapy to metformin are presented in Fig. 1b. Serious adverse events occurred in 6.6 % of empagliflozin/linagliptin 10/5 mg recipients and 4.4 % of empagliflozin/linagliptin 25/5 mg recipients compared with 4.3 % of empagliflozin 10 mg recipients, 7.1 % of empagliflozin 25 mg recipients and 6.1 % of linagliptin 5 mg recipients. Adverse events led to treatment discontinuation in 1.5, 2.2, 6.4, 2.8 and 3.0 % of patients in the corresponding treatment groups [36].

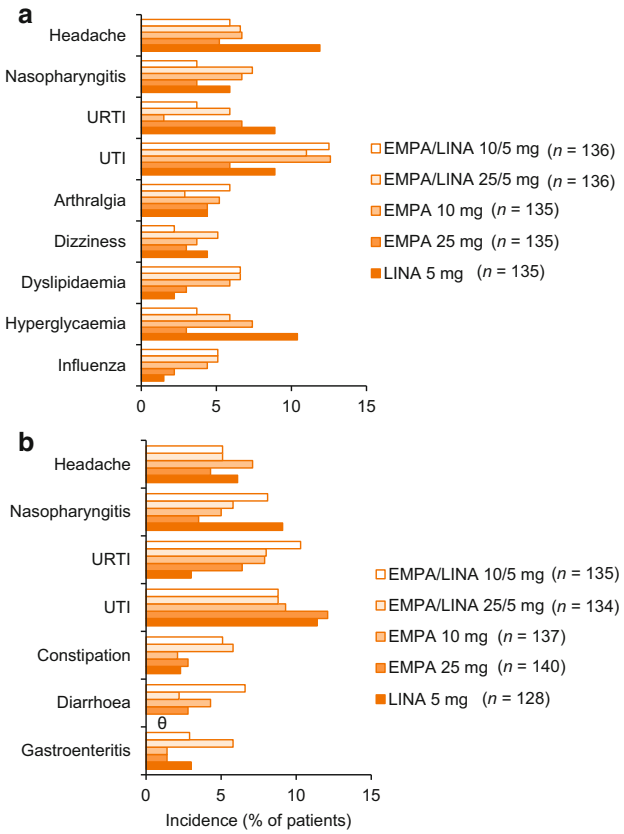

Fig. 1 Incidence of adverse events occurring in ≥5 % of empagliflozin/linagliptin 10/5 or 25/5 mg recipients and in numerically more empagliflozin/linagliptin (10/5 or 25/5 mg) recipients than empagliflozin (10 or 25 mg) or linagliptin (5 mg) recipients in the **a** initial combination therapy trial [37] and **b** add-on to metformin trial [36]. Adverse events common to both trials are listed first. *EMPA* empagliflozin, *LINA* linagliptin, *URTI* upper respiratory tract infection, *UTI* urinary tract infection. θ = 0 % incidence

5.2 Hypoglycaemia

Empagliflozin/linagliptin was associated with a low risk (<4.0 %) of hypoglycaemia when used as initial combination therapy [37] or as add-on therapy to metformin [36]. In the initial combination trial, confirmed hypoglycaemic

adverse events were reported in 0 % of empagliflozin/linagliptin 10/5 or 25/5 mg recipients compared with 3.0 % of empagliflozin 10 mg recipients, 0.7 % of empagliflozin 25 mg recipients and 0.7 % of linagliptin 5 mg recipients [37]. In the add-on to metformin trial, confirmed hypoglycaemic adverse events occurred with an incidence of 2.2 and 3.6 % with empagliflozin/linagliptin 10/5 or 25/5 mg versus 1.4 % with empagliflozin 10 mg, 3.5 % with empagliflozin 25 mg and 2.3 % with linagliptin 5 mg [36]. No assistance was required for confirmed hypoglycaemic adverse events in either trial [36, 37].

5.3 Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has occurred with linagliptin in the post-marketing setting; the clinical trial programme reported 15.2 cases of pancreatitis per 10,000 patient-years with linagliptin versus 3.7 cases per 10,000 patient-years with placebo and sulfonylurea comparators [10]. Empagliflozin/linagliptin has not been studied in patients with a history of pancreatitis; whether or not these patients are at an increased risk of developing pancreatitis during empagliflozin/linagliptin therapy is unknown [10]. One patient (empagliflozin/linagliptin 25/5 mg recipient) in the initial combination trial was reported to have pancreatitis [37]. In addition, one patient (linagliptin 5 mg recipient) in the add-on to metformin trial was reported to have chronic pancreatitis, but this was not considered to be drug related [36].

5.4 Serious Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g. anaphylaxis, angioedema, exfoliative skin conditions) have been reported in the post-marketing setting in patients taking linagliptin [10]. Hypersensitivity reactions were uncommon with empagliflozin/linagliptin (10/5 or 25/5 mg/day) and its individual components in the initial therapy (0.7 and 1.5 vs. 0–1.5 %) [37] and add-on to metformin (0.7 and 0.7 vs. 0–0.8 %) [36] trials.

5.5 Other Adverse Events of Interest

Empagliflozin is known to increase the risk of genital mycotic infections and UTIs [10]. Events consistent with genital infection occurred in fewer than 10 % of patients receiving empagliflozin/linagliptin 10/5 or 25/5 mg or the individual components in the initial combination trial (2.9 and 5.9 vs. 3.0–5.2 %) [37] or the add-on trial (5.9 and 2.2 vs. 2.3–8.5 %) [36]. Events consistent with UTIs were also reported with empagliflozin/linagliptin 10/5 or 25/5 mg or its individual components in these studies (12.5 and 15.4 vs. 10.4–16.3 % of patients in the initial combination trial [37] and 9.6 and 10.2 vs. 11.4–15.2 % in the add-on trial [36]); the incidence was numerically higher in female than male patients in all treatment groups [36, 37].

Osmotic diuresis is a potential adverse effect of SGLT2 inhibitors, including empagliflozin, that can lead to volume depletion (with an associated risk of hypotension and dizziness) [10, 40]. Events consistent with volume depletion occurred in few patients who received empagliflozin/linagliptin 10/5 or 25/5 mg or the individual components either in the initial combination trial (2.2 and 0.7 vs. 0–0 %) [37] or the add-on trial (1.5 and 0.7 vs. 0.7–3.0 %) [36].

Empagliflozin can also increase serum creatinine, decrease the eGFR and possibly increase low density lipoprotein-cholesterol (LDL-C) [10]. The treatment regimens evaluated in these trials resulted in little change from baseline to week 52 in serum creatinine, eGFR and lipids, including LDL-C, with lipid level changes not significantly differing between empagliflozin/linagliptin and its individual components [36, 37]. Hyperkalaemia is a potential adverse effect that can occur in patients taking canagliflozin, especially in patients with moderate renal impairment taking medications that interfere with potassium excretion or the renin-angiotensin-aldosterone system [41]. However, in patients receiving empagliflozin/linagliptin in the initial combination and add-on trials, potassium levels showed little change (0–0.1 mmol/L) from baseline to week 52 [36, 37].

There were no reports of exacerbations of, or hospitalizations for, heart failure in patients receiving empagliflozin/linagliptin (10/5 or 25/5 mg) or the individual components in both trials [36, 37]. In addition, there was no mention of patients experiencing changes in the heart-rate corrected QT interval or developing diabetic ketoacidosis (DKA) in the trials [36, 37]. However, the US FDA has issued a warning about the potential risk of ketoacidosis with empagliflozin, and also with canagliflozin and dapagliflozin, based on a growing number of post-marketing reports of DKA, ketoacidosis or ketosis (see Sect. 7 for further discussion) [42].

6 Dosage and Administration of Empagliflozin/Linagliptin

In adults with T2D for whom both empagliflozin and linagliptin are appropriate, the recommended starting dosage of fixed-dose oral empagliflozin/linagliptin tablets is 10/5 mg once daily, in the morning, with or without food [10]. In patients tolerating this dosage, the empagliflozin/linagliptin dosage may be increased to 25/5 mg once daily [10].

Renal function should be assessed and volume depletion corrected prior to initiating treatment [10]. Renal function should be monitored periodically thereafter, and empagliflozin/linagliptin should be discontinued if the eGFR is persistently <45 mL/min/1.73 m^2. If insulin or an insulin secretagogue is used concomitantly with empagliflozin/linagliptin, the dose of the insulin or insulin secretagogue may need to be lowered to reduce the risk of hypoglycaemia [10]. However, the lower dose of insulin may increase the rates of hepatic ketogenesis and adipose tissue lipolysis, predisposing patients to ketoacidosis [43]. If pancreatitis or a serious hypersensitivity reaction is suspected, empagliflozin/linagliptin should be discontinued promptly [10].

Contraindications include severe renal impairment, end-stage renal disease, dialysis or a history of hypersensitivity to linagliptin [10]. Local prescribing information should be consulted for further information, including dosage adjustments, interactions, contraindications, warnings and precautions.

7 Place of Empagliflozin/Linagliptin in the Management of T2D

T2D is a progressive disease with multiple pathophysiological defects (e.g. impaired insulin secretion, insulin resistance, defects in glucagon regulation, impaired incretin activity), and monotherapy is often insufficient to achieve glycaemic goals [44, 45]. Therefore, combination therapy with antihyperglycaemic agents that have complementary mechanisms of action has become a cornerstone of T2D management [45]. Among the wide array of combinations that are available, fixed-dose combinations offer the added advantage of a reduced pill burden, with the potential to offer the following benefits: reduced risk of adverse events compared with high-dose monotherapy, greater efficacy compared with high-dose monotherapy, lower costs compared with loose-pill combinations and improved medication compliance [45–47].

Empagliflozin/linagliptin is the first fixed-dose combination of an SGLT2 inhibitor and a DPP-4 inhibitor that has been approved in the USA as an adjunct to diet and exercise to improve glycaemic control in adults with T2D in whom treatment with both empagliflozin and linagliptin is appropriate [10]. In two clinical trials, oral empagliflozin/linagliptin improved glycaemic control when administered as initial combination therapy (significantly more than linagliptin; mixed results compared with empagliflozin) (Sect. 4.1) and when administered as add-on therapy to metformin (significantly more than linagliptin and empagliflozin) (Sect. 4.2), although the effects were less than the expected additive effects from each agent alone [7]. In addition to glycaemic control, empagliflozin/linagliptin provided significant weight loss compared with linagliptin in both trials. The effects of empagliflozin/linagliptin (reductions in HbA_{1c}, FPG and bodyweight) achieved at 24 weeks of treatment were maintained for the most part following 52 weeks of treatment (Sects. 4.1, 4.2). Comparative data are currently limited to comparisons with the individual components of fixed-dose empagliflozin/linagliptin, and further comparative data would be of interest.

Empagliflozin/linagliptin is generally well tolerated in patients with T2D, when used as initial combination therapy or as add-on therapy to metformin (Sect. 5). In clinical trials, most adverse events were mild to moderate in severity and deemed unrelated to the study drug (Sect. 5.1). Empagliflozin/linagliptin was associated with a low risk of hypoglycaemia (Sect. 5.2), and there were no reports of exacerbations of, or hospitalizations for, heart failure during the trials (Sect. 5.5).

An increased risk of hospitalizations for heart failure is a new concern that has emerged with DPP-4 inhibitors [4]. In SAVOR-TIMI 53, a trial comparing saxagliptin with placebo in patients with T2D at risk of, or with a history of, cardiovascular events ($n = 16{,}492$), significantly ($p = 0.007$) more patients receiving saxagliptin were hospitalized for heart failure compared with those receiving placebo [48]. In addition, a recent meta-analysis of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin and vildagliptin, showed an increased signal ($p = 0.017$) of hospitalizations for heart failure [49]. However, data for the meta-analysis were dominated by that of SAVOR-TIMI 53 [48], without which analysis of the remaining studies showed a nonsignificant increase [49]. A post-hoc analysis of EXAMINE, a trial comparing alogliptin with placebo in T2D patients with a recent acute coronary syndrome event ($n = 5380$), showed that alogliptin had no effect on hospital admissions for heart failure [50], and TECOS, a trial comparing sitagliptin with placebo in T2D patients with cardiovascular disease, showed no significant between-group difference in rates of hospitalization for heart failure [51]. In addition, a post-hoc pooled analysis of 22 randomized, double-blind, placebo-controlled, phase I-III trials of T2D patients ($n = 7400$) did not show an increased risk for heart failure in linagliptin recipients [52]. Establishing the cardiac safety of antidiabetic drugs is of particular importance in T2D patients because they are already at an increased risk for cardiovascular disease [27], and the results of ongoing trials investigating long-term cardiovascular outcomes of linagliptin [NCT01897532

(CARMELINA®), NCT01243424 (CAROLINA™)] and empagliflozin [NCT01131676 (EMPA-REG OUTCOME™)] in T2D patients are awaited with interest.

Serious and sometimes life-threatening cases of DKA in patients under treatment with SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) have been reported, with the majority of them requiring hospitalization [42, 53, 54]. The FDA identified 20 reported cases of DKA, ketoacidosis or ketosis in a period of ≈15 months, with a median time from initiation of SGLT2 inhibitor therapy to onset of symptoms of 2 weeks [42]. Most of these cases involved patients with T2D, and a few involved off-label use in patients with type 1 diabetes. Potential triggers in some cases included acute illness, reduced insulin dose and reduced food and fluid intake [42]. In a number of cases, atypical moderately increased glucose values <200 mg/dL were reported [42]. Of note, there have been case reports of euglycaemic ketoacidosis with canagliflozin [43, 55]. The FDA is continuing to investigate the issue and is considering whether labelling changes are needed for the drug class [42].

Current guidelines from the American Diabetes Association (ADA) [5] and the ADA, together with the European Association for the Study of Diabetes (EASD) [4], recommend a stepwise treatment approach for T2D. Most patients begin with lifestyle changes, and pharmacological therapy with metformin (preferred first-line agent) is started at, or soon after, diagnosis, in order to achieve or maintain glycaemic goals (generally HbA_{1c} <7.0 % for nonpregnant adults) [4, 5]. In the event that a patient has contraindications or intolerances to metformin, initial therapy is started with one of the following options: a DPP-4 inhibitor, GLP-1 receptor agonist, basal insulin, SGLT2 inhibitor, sulfonylurea or thiazolidinedione. Combination therapy (dual, then triple) is typically considered if the HbA_{1c} target is not reached after ≈3 months on monotherapy or if HbA_{1c} is ≥9 % [4, 5].

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines [56, 57] differ slightly from those of the ADA and the EASD in that T2D patients with baseline HbA_{1c} <7.5 % are recommended to start initial monotherapy (alongside lifestyle modifications) with one of the following OADs (listed in preferential order): metformin, a GLP-1 receptor agonist, a SGLT2 or DPP-4 inhibitor or an α-glucosidase inhibitor. Patients with baseline HbA_{1c} ≥7.5 % are recommended to start initial combination therapy with metformin (unless contraindicated) and one of the following agents (listed in preferential order): a GLP-1 receptor agonist, a SGLT2 inhibitor or a DPP-4 inhibitor. Patients with baseline HbA_{1c} >9 % with symptoms of hyperglycaemia are recommended to start insulin, either as monotherapy or as combination therapy with metformin or other OAD. Of note, the general glycaemic goal in the AACE/ACE guidelines for T2D patients with low hypoglycaemic risk and without concurrent serious illness is HbA_{1c} ≤6.5 % [56, 57]. For patients for whom empagliflozin and linagliptin are appropriate, the fixed-dose empagliflozin/linagliptin tablet may potentially provide a more convenient alternative to the individual agents.

The topic of initial combination therapy is an area of growing interest [44, 58]. Results from a systematic review and meta-analysis of 15 randomized controlled trials suggested a potential benefit (improved glycaemic outcomes including significant HbA_{1c} reductions) with initial metformin combination therapy over metformin monotherapy in untreated T2D patients with a wide range of baseline HbA_{1c} levels [58]. The need for a paradigm shift in the management of T2D remains to be demonstrated by long-term clinical trials comparing various initial combination therapies with the traditional stepwise approach [44].

In conclusion, empagliflozin/linagliptin is a useful new option for patients with T2D. It is the first SGLT2 inhibitor/DPP-4 inhibitor fixed-dose combination available for use in this setting, combining two recently approved medications with proven and complementary mechanisms of action in an effective, generally well tolerated and convenient once-daily tablet.

Data selection sources:

Relevant medical literature (including published and unpublished data) on empagliflozin/linagliptin was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 3 August 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Empagliflozin, BI-10773, linagliptin, BI-1356, Glyxambi.
Study selection: Studies in patients with type 2 diabetes who received empagliflozin/linagliptin. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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