Jardiance® Duo
Empagliflozin and Metformin hydrochloride

COMPOSITION

1 film-coated tablet contains:

D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S) (= empagliflozin) 5 or 12.5 mg and N,N-dimethylimidodicarbonimidic diamide hydrochloride (= metformin hydrochloride) 500 mg, 850 mg, or 1000 mg

INDICATIONS

Jardiance Duo is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control

- in patients inadequately controlled on their maximally tolerated dose of metformin alone
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

DOSAGE AND ADMINISTRATION

Adults with normal renal function (GFR ≥ 90ml/min)

The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability. The maximum recommended daily dose of Jardiance Duo 25 mg of empagliflozin and 2000 mg of metformin.

In patients not adequately controlled on metformin alone, the recommended starting dose of Jardiance Duo should provide empagliflozin 5 mg twice daily (10 mg total daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating a total daily dose of empagliflozin 10 mg, the dose can be increased to a total daily dose of empagliflozin 25 mg.

- Patients already treated with empagliflozin should continue to take the same daily dose of empagliflozin.

- Patients switching from separate tablets of empagliflozin (10 mg or 25 mg total daily dose) and metformin to Jardiance Duo should receive the same daily dose of empagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

The recommended dose is one tablet twice daily.
For the different doses of metformin, Jardiance Duo is available in strengths of 5 mg empagliflozin plus 500 mg metformin hydrochloride or 12.5 mg empagliflozin plus 500 mg, 850 mg or 1000 mg metformin hydrochloride.

Jardiance Duo should be given with meals to reduce the gastrointestinal undesirable effects associated with metformin.

<u>Renal impairment</u>
No dose adjustment is recommended for patients with mild renal impairment.
A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal

impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Missed dose
If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken at the same time. In that case, the missed dose should be skipped.

Paediatric population
Jardiance Duo is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

CONTRAINDICATIONS

- Hypersensitivity to active ingredients empagliflozin and/or metformin or to any of the excipients (see section Composition)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Moderate and severe renal failure or renal dysfunction (CrCl <60 ml/min or eGFR <60 ml/min/1.73m^2), due to its metformin component.
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see section Special warnings and precautions)
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (see section Interactions)
- Major surgery

SPECIAL WARNINGS AND PRECAUTIONS

General
Jardiance Duo should not be used in patients with type 1 diabetes.

Diabetic ketoacidosis
Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients treated with empagliflozin, including fatal cases. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl).

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.

Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. If ketoacidosis is suspected, Jardiance Duo should be discontinued, patient should be evaluated, and prompt treatment should be instituted.

Patients who may be at higher risk of ketoacidosis while taking Jardiance Duo include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g. type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration, and patients with a history of ketoacidosis. Jardiance Duo should be used with caution in these patients. When reducing the insulin dose caution should be taken. In patients treated with Jardiance Duo consider monitoring for ketoacidosis and temporarily discontinuing Jardiance Duo in clinical situations

known to predispose to ketoacidosis (e.g. prolonged fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if Jardiance Duo treatment has been interrupted.

Lactic acidosis
Lactic acidosis, a very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients.

Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see section Contraindications and Interactions).

Patients and/or care-givers should be informed of the risk of lactic acidosis.

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.

Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (> 5 mmol/l), and an increased anion gap and lactate/pyruvate ratio.

Administration of iodinated contrast agent
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections Posology and Interactions.

Necrotizing fasciitis of the perineum (Fournier's gangrene)
Postmarketing cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with Jardiance Duo who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotizing fasciitis. If suspected, Jardiance Duo should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Renal function
Due to the mechanism of action, the efficacy of empagliflozin is dependent on renal function. GFR should be assessed before treatment initiation and regularly thereafter, see section Posology. Jardiance Duo is contraindicated in patients with GFR<60 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section Contraindications.

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure, Jardiance Duo may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, Jardiance Duo is contraindicated due to the metformin component (see section Contraindications).

Elderly patients
Patients aged 75 years and older may be at an increased risk of volume depletion, therefore, Jardiance Duo should be prescribed with caution in these patients (see section Side effects). Therapeutic experience in patients aged 85 years and older is limited. Initiation of treatment in this population is not recommended.

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Jardiance Duo should have their renal function monitored regularly.

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status.

Use in patients at risk for volume depletion
Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with Jardiance Duo should be considered until the fluid loss is corrected.

Urinary tract infections
In the pooled placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was higher in patients treated with empagliflozin 10 mg plus metformin as compared to patients treated with placebo plus metformin or empagliflozin 25 mg plus metformin (see section Side Effects).
Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of treatment should be considered in patients with complicated urinary tract infections.

Surgery
Jardiance Duo must be discontinued at the time of urgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Elevated haematocrit
Haematocrit increase was observed with empagliflozin treatment

Urine laboratory assessments
Due to its mechanism of action, patients taking Jardiance Duo will test positive for glucose in their urine.

Urosepsis and Pyelonephritis
There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. Discontinuation of Jardiance Duo may be considered in cases of recurrent urinary tract infections.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in a long-term clinical study with another SGLT2 inhibitor. The medicine in that study is not empagliflozin. However, it is unknown whether this constitutes a class effect. In a pooled safety analysis of 12,620 patients with T2DM the frequency of patients with lower limb amputations was similar between empagliflozin and placebo. In the largest placebo-controlled trial in 7020 patients (EMPA-REG OUTCOME trial), in which 88% of all the cases of amputations were reported, lower limb amputations occurred in 1.8% of patients treated with empagliflozin 10 mg, in 2.0% of patients treated with empagliflozin 25 mg, and in 1.8% of patients in the placebo arm. It is important to regularly examine the feet and counsel all diabetic patients on routine preventative footcare.

Vitamin B12 levels
In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels,without clinical manifestations, was observed in approximately 7% of patients. Such decrease,possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on JARDIAMET and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

USE IN SPECIFIC POPULATIONS

Fertility, Pregnancy and Lactation

Pregnancy
There are no data from the use of this medicinal product or empagliflozin in pregnant women. Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development. A limited amount of data suggests that the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with the combination of empagliflozin and metformin or with metformin alone have shown reproductive toxicity at higher doses of metformin only. When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product.

Lactation
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. It is unknown whether empagliflozin is excreted in human milk.

Available nonclinical data in animals have shown excretion of empagliflozin in milk. A risk to human newborns/infants cannot be excluded. It is recommended to discontinue breast feeding during treatment with Jardiance Duo.

Fertility
No studies on the effect on human fertility have been conducted with Jardiance Duo or its individual components.

Non-clinical studies in animals with the individual components do not indicate direct or indirect harmful effects with respect to fertility.

Driving and Using Machines
No studies on the effects on the ability to drive and use machines have been performed.

INTERACTIONS

Empagliflozin

Pharmacodynamic Interactions
Diuretics
Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin Secretagogues
insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a *lower dose* of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin (see Side effects). However, combination of Jardiance Duo with insulin or an insulin secretagogue is not indicated.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay
Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Pharmacokinetic Interactions
In vitro assessment of drug interactions
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7.
Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. At therapeutic doses, the potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 isoforms or UGT1A1 is remote. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

In vivo assessment of drug interactions
No clinically meaningful pharmacokinetic interactions were observed when empagliflozin was coadministered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of empagliflozin is recommended when co-administered with commonly prescribed medicinal products.

Empagliflozin pharmacokinetics were similar with and without co-administration of glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, in

healthy volunteers and with or without co-administration of torasemide and hydrochlorothiazide in patients with T2DM. Increases in overall exposure (AUC) of empagliflozin were seen following co-administration with gemfibrozil (59%), rifampicin (35%), or probenecid (53%). These changes were not considered to be clinically meaningful

Empagliflozin had no clinically relevant effect on the pharmacokinetics of glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

Metformin

Concomitant use not recommended

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis particularly in cases of fasting, malnutrition or hepatic insufficiency.

Iodinated contrast agents
Jardiance Duo must be discontinued prior to or at the time of the imaging procedure and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see section Posology and Special warnings and precautions).

Combination requiring precautions for use
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Glucocorticoids (given by systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with:
- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

SIDE EFFECTS

A total of 12245 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin plus metformin. In these trials 2910 patients received treatment with empagliflozin 10 mg plus metformin and 3699 patients treatment with empagliflozin 25 mg plus metformin for at least 24 weeks and 2151 or 2807 patients for at least 76 weeks.
The overall safety profile of empagliflozin plus metformin for patients enrolled in the EMPA-REG OUTCOME study was comparable to the previously known safety profile.

Placebo-controlled, double-blind trials of 18 to 24 weeks of exposure included 3456 patients, of which 1271 were treated with empagliflozin 10 mg plus metformin and 1259 with empagliflozin 25 mg plus metformin.

The most frequently reported adverse event in clinical trials was hypoglycaemia, which depended on the type of background therapy used in the respective studies (see description of selected side effects).

No additional side effects were identified in clinical trials with empagliflozin plus metformin compared to the side effects of the single components.

Table 1 Side effects reported in patients who received empagliflozin monotherapy or combination therapy of empagliflozin and metformin in placebo controlled double-blind studies of up to 24 weeks (regardless of investigator reported causality assessment), and side effects derived from postmarketing experience with empagliflozin monotherapy or combination therapy of empagliflozin and metformin, classified by MedDRA System organ class and MedDRA Preferred terms

System Organ class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[1, 2] Urinary tract infection (including pyelonephritis and urosepsis)[1, 2]				Necrotizing fasciitis of the perineum (Fournier´s gangrene)[2,6]
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[1]	Thirst[2]		Diabetic Ketoacidosis [a]	Lactic acidosis[3] Vitamin B12 deficiency[3, 4]	
Nervous system disorders		Taste disturbance[3]				
Vascular disorders			Volume depletion[1,2]			
Gastrointestinal disorders[5]	Gastrointestinal symptoms[3, 5]	Constipation				
Hepatobiliary disorders					Liver function tests abnormalities[3], Hepatitis[3]	
Skin and subcutaneous tissue disorders		Pruritus (generalised)[2, 3] Rash	Urticaria		Erythema[3]	Angioedema
Renal and urinary disorders		Increased urination[1,2]	Dysuria[2]			

System Organ class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Investigations		Serum lipids increased[2,b]	Blood creatinine increased/ Glomerular filtration rate decreased[1] Haematocrit increased[2, c]			

1 See subsections below for additional information
2 Identified side effect of empagliflozin monotherapy
3 Identified side effect of metformin monotherapy
4 Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia)
5 Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
6 Identified adverse reactions from postmarketing experience
a See section Special warning and precautions
b Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 5.0% and 5.2% versus 3.7%; HDL-cholesterol 4.6% and 2.7% versus -0.5%; LDL-cholesterol 9.1% and 8.7% versus 7.8%; triglycerides 5.4% and 10.8% versus 12.1%.
c Mean changes from baseline in haematocrit were 3.6% and 4.0% for empagliflozin 10 mg and 25 mg,
respectively, compared to 0% for placebo. In the EMPA-REG Outcome study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

Description of selected side effects

The frequencies below are calculated for side effects regardless of causality.

Hypoglycaemia
The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar to placebo for empagliflozin as add-on to metformin and as add-on to pioglitazone +/- metformin, and as add-on with linagliptin + metformin. The frequency of patients with hypoglycaemia was increased in patients treated with empagliflozin compared to placebo when given as add-on to metformin plus sulfonylurea, and as add-on to insulin +/- metformin and +/-sulfonylurea. (see Table 2 below)

Major hypoglycaemia (events requiring assistance)
The overall frequency of patients with major hypoglycaemic events was low (<1%) and similar for empagliflozin and placebo as add-on to metformin compared to those treated with empagliflozin and metformin as individual components, and as adjunct to standard care therapy. Major hypoglycaemic events occurred in 0.5%, 0% and 0.5% of patients treated with empagliflozin 10mg, empagliflozin 25mg and placebo when added on to metformin and insulin, respectively. (see Table 2 below)

Table 2 Frequency of patients with confirmed hypoglycaemic events per trial and indication (1245.19, 1245.23(met), 1245.23(met+SU), 1245.33, 1245.49, 1276.1, 1276.10, 1275.9, and 1245.25 – TS[1])

Treatment group	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
In combination with metformin (1245.23 *(met)*) (24 weeks)			
N	**206**	**217**	**214**
Overall confirmed (%)	0.5%	1.8%	1.4%
Major (%)	0%	0%	0%
In Combination with Metformin + Sulfonylurea (1245.23 *(met + SU)*) (24 weeks)			
N	**225**	**224**	**217**
Overall confirmed (%)	8.4%	16.1%	11.5%
Major (%)	0%	0%	0%
In Combination with Pioglitazone +/- Metformin (1245.19) (24 weeks)			
N	**165**	**165**	**168**
Overall confirmed (%)	1.8%	1.2%	2.4%
Major (%)	0%	0%	0%
In Combination with Basal Insulin +/- Metformin +/-sulfonylurea (1245.33) (18 weeks[2] / 78 weeks)			
N	**170**	**169**	**155**
Overall confirmed (%)	20.6% / 35.3%	19.5% / 36.1%	28.4% / 36.1%
Major (%)	0% / 0%	0% / 0%	1.3% / 1.3%
In Combination with MDI Insulin +/-Metformin (1245.49) (18 weeks[2] / 52 weeks)			
N	**188**	**186**	**189**
Overall confirmed (%)	37.2% / 58.0%	39.8% / 51.1%	41.3% / 57.7%
Major (%)	0.5% / 1.6%	0.5% / 1.6%	0.5% / 0.5%
Empagliflozin BID versus QD as add on to metformin (1276.10) (16 weeks)			
	Placebo	**Empa 10 mg**	**Empa 25 mg**
N	**107**	**439**	**437**
Overall confirmed (%)	0.9%	0.5%	0.2%
Major (%)	0%	0%	0%
In Combination with metformin in drug-naïve patients (1276.1[3]) (24 weeks)			
	Met 500/1000 mg BID	**Empa 10/25 mg QD**	**Empa (5/12.5 mg) + Met (500/1000 mg) BID**
N	**341**	**339**	**680**
Overall confirmed (%)	0.6%	0.6%	1.0%
Major (%)	0%	0%	0%
In Combination with metformin and linagliptin (1275.9) (24 weeks)[3]			
N	**110**	**112**	**110**
Overall confirmed (%)	0.9%	0.0%	2.7%
Major (%)	0%	0%	0.9%
EMPA REG OUTCOME Study (1245.25)			
	Placebo	**Empa 10 mg**	**Empa 25 mg**
N	**2333**	**2345**	**2342**
Overall confirmed (%)	27.9%	28%	27.6%
Major (%)	1.5%	1.4%	1.3%

Confirmed: blood glucose ≤70 ml/dL or required assistance
Major: required assistance
[1]i.e. patients who had received at least one dose of study drug
[2]The dose of insulin as background medication was to be stable for the first 18 weeks
[3]Eight treatment arms: 4 combination treatments of empagliflozin (5 mg or 12.5 mg BID) and metformin (500 or 1000 mg BID) and treatment with the individual components of empagliflozin (10 mg or 25 mg QD) or metformin (500 mg or 1000 mg BID).
[3]This was a fixed-dose combination of empagliflozin with linagliptin 5 mg with a background treatment with metformin. (see also Clinical Trials section).

Urinary tract infection
The overall frequency of urinary tract infection adverse events was higher in patients treated with empagliflozin 10 mg plus metformin (8.8%) as compared to empagliflozin 25 mg plus metformin (6.6%) or placebo plus metformin (7.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin plus metformin in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections was similar to placebo. Urinary tract infection events were reported more frequently for empagliflozin 10 mg plus metformin compared with placebo in female patients, but not for empagliflozin 25 mg plus metformin. The frequencies of urinary tract infections were low for male patients and were balanced across treatment groups.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg plus metformin (4.0%) and empagliflozin 25 mg plus metformin (3.9%) compared to placebo plus metformin (1.3%), and were reported more frequently for empagliflozin plus metformin compared to placebo in female patients. The difference in frequency was less pronounced in male patients. Genital tract infections were mild and moderate in intensity, none was severe in intensity.

Increased urination
As expected via its mechanism of action, increased urination (as assessed by PT search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin 10 mg plus metformin (3.0%) and empagliflozin 25 mg plus metformin (2.9%) compared to placebo plus metformin (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin, both on a background of metformin (<1%).

Volume depletion
The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was low and comparable to placebo (empagliflozin 10 mg plus metformin (0.6%), empagliflozin 25 mg plus metformin (0.3%) and placebo plus metformin (0.1%). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status of patients aged 75 years and older. In patients ≥75 years of age, volume depletion events have been reported in a single patient treated with empagliflozin 25 mg plus metformin.

Blood creatinine increased and glomerular filtration rate decreased
The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between empagliflozin and placebo as add-on to metformin (blood creatinine increased: empagliflozin 10 mg 0.5%, empagliflozin 25 mg 0.1%, placebo 0.4%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.2%).
In these placebo-controlled, double-blind studies up to 24 weeks, initial transient increases in creatinine (mean change from baseline after 12 weeks: empagliflozin 10 mg 0.02 mg/dL, empagliflozin 25 mg 0.02 mg/dL) and initial transient decreases in estimated glomerular filtration rates (mean change from baseline after 12 weeks: empagliflozin 10 mg -1.46

mL/min/1.73m2, empagliflozin 25 mg -2.05 mL/min/1.73m2) have been observed. In the long term studies, these changes were generally reversible during continuous treatment or after drug discontinuation (see section Clinical Trials figure 6 for the eGFR course in the EMPA-REG outcome study).

OVERDOSE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg empagliflozin, equivalent to 32 times the maximum recommended daily dose, were well tolerated.

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Therapy
In the event of an overdose, supportive treatment should be initiated as appropriate to the patient's clinical status. The most effective method to remove lactate and metformin hydrochloride is haemodialysis whereas removal of empagliflozin by haemodialysis has not been studied.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD20

Mode of Action

Jardiance Duo combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), and metformin hydrochloride, a member of the biguanide class.

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC_{50} of 6278 nM), responsible for glucose absorption in the gut. Furthermore high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues.

SGLT-2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR. Through inhibition of SGLT-2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

In patients with T2DM, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24-hour dosing interval. Increased urinary glucose excretion was maintained at the end of 4-week treatment period, averaging approximately 78 g/day with 25 mg empagliflozin once daily. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with T2DM.

Empagliflozin improves both fasting and post-prandial plasma glucose levels.

The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia.

Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-B (HOMA-β) and proinsulin to insulin ratio were noted. In addition urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction.

The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.
Metformin hydrochloride may act via 3 mechanisms:

(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
(3) and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane GLUTs known to date.

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium- or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical Trials

A total of 10224 patients with type 2 diabetes were treated in 9 double-blind, placebo- or active-controlled clinical studies of at least 24 weeks duration, of which 2947 patients received empagliflozin 10 mg and 3703 received empagliflozin 25 mg as add-on to metformin therapy. Treatment with empagliflozin in combination with metformin with or without other background (pioglitazone, sulfonylurea, DPP-4 inhibitors, and insulin) led to clinically relevant improvements in HbA_{1c}, fasting plasma glucose, body weight, systolic and diastolic blood pressure. Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA_{1c} goal of < 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. There was a clinically meaningful improvement in HbA_{1c} in all subgroups of gender, race, geographic region, time since diagnosis of T2DM and body mass index (BMI). In patients aged 75 years and older, numerically lower reductions in HbA_{1c} were observed with empagliflozin treatment. Higher baseline HbA_{1c} was associated with a greater reduction in HbA_{1c}. Empagliflozin in combination with metformin in drug-naïve patients led to clinically meaningful reductions in HbA_{1c}, FPG, body weight and BP.

Empagliflozin as add on to metformin therapy
A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients not sufficiently treated with metformin. Treatment with empagliflozin resulted in statistically significant improvements in HbA_{1c} and body weight, and clinically meaningful reductions in FPG and blood pressure compared to placebo (Table 3).

In the double-blind placebo-controlled extension of this study, reductions of HbA_{1c} (change from baseline of -0.62% for empagliflozin 10 mg, -0.74% for empagliflozin 25 mg and -0.01% for placebo), body weight (change from baseline of -2.39 kg for empagliflozin 10 mg, -2.65 kg for empagliflozin 25 mg and -0.46 kg for placebo) and blood pressure (SBP: change from baseline of -5.2 mmHg for empagliflozin 10 mg, -4.5 mmHg for empagliflozin 25 mg and -0.8 mmHg for placebo, DBP: change from baseline of -2.5 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg and -0.5 mmHg for placebo) were sustained up to Week 76.

Table 3 Results of a 24-week (LOCF)[3] placebo-controlled study of empagliflozin as add-on to metformin (Full Analysis Set)

Empagliflozin as add-on to metformin therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	207	217	213
HbA1c (%)			
Baseline (mean)	7.90	7.94	7.86
Change from baseline[1]	-0.13	-0.70	-0.77
Difference from placebo[1] (97.5% CI)		-0.57* (-0.72, -0.42)	-0.64* (-0.79, -0.48)
N	184	199	191
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	12.5	37.7	38.7
N	207	216	213
FPG (mg/dL) [mmol/l][2]			
Baseline (mean)	156.0 [8.66]	154.6 [8.58]	149.4 [8.29]
Change from baseline[1]	6.4 [0.35]	-20.0 [-1.11]	-22.3 [-1.24]
Difference from placebo[1] (95% CI)		-26.4* (-31.3, -21.6) [-1.47* (-1.74, -1.20)]	-28.7* (-33.6, -23.8) [-1.59* (-1.86, -1.32)]
N	207	217	213
Body Weight (kg)			
Baseline (mean)	79.73	81.59	82.21
Change from baseline[1]	-0.45	-2.08	-2.46
Difference from placebo[1](97.5% CI)		-1.63* (-2.17, -1.08)	-2.01* (-2.56, -1.46)
N	207	217	213
Patients (%) achieving weight loss of >5%[2]	4.8	21.2	23.0
N	207	217	213
SBP (mmHg)[2]			
Baseline (mean)	128.6	129.6	130.0
Change from baseline[1]	-0.4	-4.5	-5.2
Difference from placebo[1] (95% CI)		-4.1* (-6.2, -2.1)	-4.8* (-6.9, -2.7)

[1] mean adjusted for baseline value and stratification
[2] not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[3] Last observation (prior to glycemic rescue) carried forward (LOCF)
*p-value <0.0001

Empagliflozin 2-year data, as add on to metformin in comparison to glimepiride
In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (4 mg) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA_{1c}, and a clinically meaningful reduction in FPG, compared to glimepiride (Table 9). Empagliflozin daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure (change from baseline in DBP of -1.8 mmHg for empagliflozin and +0.9 mmHg for glimepiride, p<0.0001).

Treatment with empagliflozin resulted in statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride, p<0.0001).

Table 4 Results at 104 week (LOCF)[4] in an active controlled study comparing empagliflozin to glimepiride as add on to metformin (Full Analysis Set)

Empagliflozin as add-on to metformin therapy in comparison to glimepiride	**Empagliflozin 25 mg**	**Glimepiride (up to 4 mg)**
N	765	780
HbA1c (%)		
Baseline (mean)	7.92	7.92
Change from baseline[1]	-0.66	-0.55
Difference from glimepiride[1](97.5%) CI)	-0.11* (-0.20, -0.01)	
N	690	715
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	33.6	30.9
N	764	779
FPG (mg/dL)[2]		
Baseline (mean)	150.00	149.82
Change from baseline[1]	-15.36	-2.98
Difference from glimepiride[1] (95% CI)	-12.37** (-15.47,-9.27)	
N	765	780
Body Weight (kg)		
Baseline (mean)	82.52	83.03
Change from baseline[1]	-3.12	1.34
Difference from glimepiride[1] (97.5% CI)	-4.46** (-4.87, -4.05)	
N	765	780
Patients(%) achieving weight loss of >5%[2]	27.5	3.8%
N	765	780
SBP (mmHg)[3]		
Baseline (mean)	133.4	133.5
Change from baseline[1]	-3.1	2.5
Difference from glimepiride[1] (97.5% CI)	-5.6** (-7.0,-4.2)	

[1] Mean adjusted for baseline value and stratification
[2] Not evaluated for statistical significance; not part of the sequential testing procedure for the secondary endpoints
[3] LOCF, values after antihypertensive rescue censored
[4] Last observation (prior to glycemic rescue) carried forward (LOCF)
* p-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority
** p-value <0.0001

Empagliflozin twice daily versus once daily as add on to metformin therapy
The efficacy and safety of empagliflozin twice daily versus once daily (daily dose of 10 mg and 25 mg) as add-on therapy in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo-controlled study of 16 weeks duration. All treatments with empagliflozin resulted in significant reductions in HbA_{1c} from baseline (total mean 7.8%) after 16 weeks of treatment compared with placebo. Empagliflozin twice daily dose regimens led to comparable reductions in HbA_{1c} versus once daily dose regimens with a treatment difference in HbA_{1c} reductions from baseline to week 16 of -0.02% (95% CI -0.16, 0.13) for empagliflozin 5 mg twice daily vs. 10 mg once daily, and -0.11% (95% CI -0.26, 0.03) for empagliflozin 12.5 mg twice daily vs. 25 mg once daily.

<u>2-hour postprandial glucose</u>

Treatment with empagliflozin as add-on to metformin resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin, placebo (n=57): +5.9 mg/dL, empagliflozin 10 mg (n=52): -46.0 mg/dl, empagliflozin 25 mg (n=58): -44.6 mg/dL;

Patients with baseline HbA1c ≥9%
In a pre-specified analysis of subjects with baseline HbA_{1c} ≥9.0%, treatment with empagliflozin 10 mg or 25 mg as add-on to metformin resulted in statistically significant reductions in HbA_{1c} at Week 24 (adjusted mean change from baseline of -1.49% for empagliflozin 25 mg, -1.40% for empagliflozin 10 mg, and -0.44% for placebo).

Body weight
In a pre-specified pooled analysis of 4 placebo controlled studies, treatment with empagliflozin (68% of all patients were on metformin background) resulted in body weight reduction compared to placebo at week 24 (-2.04 kg for empagliflozin 10 mg, -2.26 kg for empagliflozin 25 mg and -0.24 kg for placebo) that was maintained up to week 52 (-1.96 kg for empagliflozin 10 mg, -2.25 kg for empagliflozin 25 mg and -0.16 kg for placebo).

Blood pressure
The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo-controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic (67.8% treated with metformin with or without other antidiabetic drugs including insulin) and up to 2 antihypertensive therapies (Table 10). Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA_{1c}, 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring. Treatment with empagliflozin provided reductions in seated SBP (change from baseline of -0.67 mmHg for placebo, -4.60 mmHg for empagliflozin 10 mg and -5.47 mmHg for empagliflozin 25 mg) and seated DBP (change from baseline of -1.13 mmHg for placebo, -3.06 mmHg for empagliflozin 10 mg and -3.02 mmHg for empagliflozin 25 mg).

Table 5 Results at 12 week (LOCF)[3] in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure (Full Analysis Set)

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	271	276	276
HbA1c (%) at week 12			
Baseline (mean)	7.90	7.87	7.92
Change from baseline[1]	0.03	-0.59	-0.62
Difference from placebo[1] (95% CI)		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour SBP at week 12[2]			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[1]	0.48	-2.95	-3.68
Difference from placebo[1] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour DBP at week 12[2]			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[1]	0.32	-1.04	-1.40
Difference from placebo[1] (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

[1] Mean adjusted for baseline value and stratification
[2] Last observation (prior to antihypertensive rescue) carried forward (LOCF) LOCF, values after antihypertensive rescue censored value
[3] Last observation (prior to glycemic rescue) carried forward (LOCF)
* p-value <0.0001
** p-value =0.0008

In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin (68% of all patients were on metformin background) resulted in a reduction in systolic blood pressure (empagliflozin 10 mg -3.9 mmHg, empagliflozin 25 mg -4.3 mmHg) compared with placebo (-0.5 mmHg), and in diastolic blood pressure (empagliflozin 10 mg -1.8 mmHg, empagliflozin 25 mg -2.0 mmHg) compared with placebo (-0.5 mmHg), at week 24, that were maintained up to week 76.

Cardiovascular outcome
The EMPA-REG OUTCOME study is a multi-centre, multi-national, randomized, double-blind, placebo-controlled trial investigating the effect of empagliflozin as adjunct to standard care therapy in reducing cardiovascular events in patients with type 2 diabetes and one or more cardiovascular risk factors, including coronary artery disease, peripheral artery disease, history of myocardial infarction (MI), or history of stroke. The primary endpoint was the time to first event in the composite of CV death, nonfatal MI, or non-fatal stroke (Major Adverse Cardiovascular Events (MACE-3). Additional pre-specified endpoints addressing clinically relevant outcomes tested in an exploratory manner included CV death, the composite of heart failure requiring hospitalization or CV death, all-cause mortality and the composite of new or worsening nephropathy.

A total of 7020 patients were treated with empagliflozin (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years.
The population was 72.4% Caucasian, 21.6% Asian, and 5.1% Black. The mean age was 63 years and 71.5% were male. At baseline, approximately 81% of patients were being treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 89% with anticoagulants, and 81% with lipid lowering medication. Approximately 74% of patients were being treated with metformin at baseline, 48% with insulin and 43% with sulphonylurea.

About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 m^2, 17.8% of 45-60 ml/min/1.73 m^2 and 7.7% of 30-45 ml/min/1.73 m^2. Mean systolic BP was 136 mmHg, diastolic BP 76 mmHg, LDL 86 mg/dL, HDL44 mg/dL, and urinary albumin to creatinine ratio (UACR) 175 mg/g at baseline.

Reductions in risk of CV death and overall mortality
Empagliflozin is superior in reducing the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke compared to placebo. The treatment effect reflected a reduction in cardiovascular death with no significant change in non-fatal MI, or non-fatal stroke (Table 11 and Figure 1).

Empagliflozin also improved overall survival (Table 11 and Figure 2), which was driven by a reduction in cardiovascular death with empagliflozin. There was no statistically significant difference between empagliflozin and placebo in non-cardiovascular mortality.

Table 6 Treatment effect for the primary composite endpoint, its components and mortality (Treated Set*)

	Placebo	**Empagliflozin (10 and 25 mg, pooled)**
N	2333	4687
Time to first occurence of CV death, non-fatal MI, or non-fatal stroke) N (%)	282 (12.1)	490 (10.5)
Hazard ratio vs. placebo (95.02% CI)**		0.86 (0.74, 0.99)
p-value for superiority		0.0382
CV Death N (%)	137 (5.9)	172 (3.7)
Hazard ratio vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		<0.0001
Non-fatal MI N (%)	121 (5.2)	213 (4.5)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.09)
p-value		0.2189
Non-fatal stroke N (%)	60 (2.6)	150 (3.2)
Hazard ratio vs. placebo (95% CI)		1.24 (0.92, 1.67)
p-value		0.1638
All-cause mortality N (%)	194 (8.3)	269 (5.7)
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
Non-CV mortality N (%)	57 (2.4)	97 (2.1)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.16)

* i.e. patients who had received at least one dose of study drug

**Since data from the trial were included in an interim analysis, a two-sided 95.02% confidence interval applied which corresponds to a p-value of less than 0.0498 for significance.

Figure 1 Time to occurrence of CV death

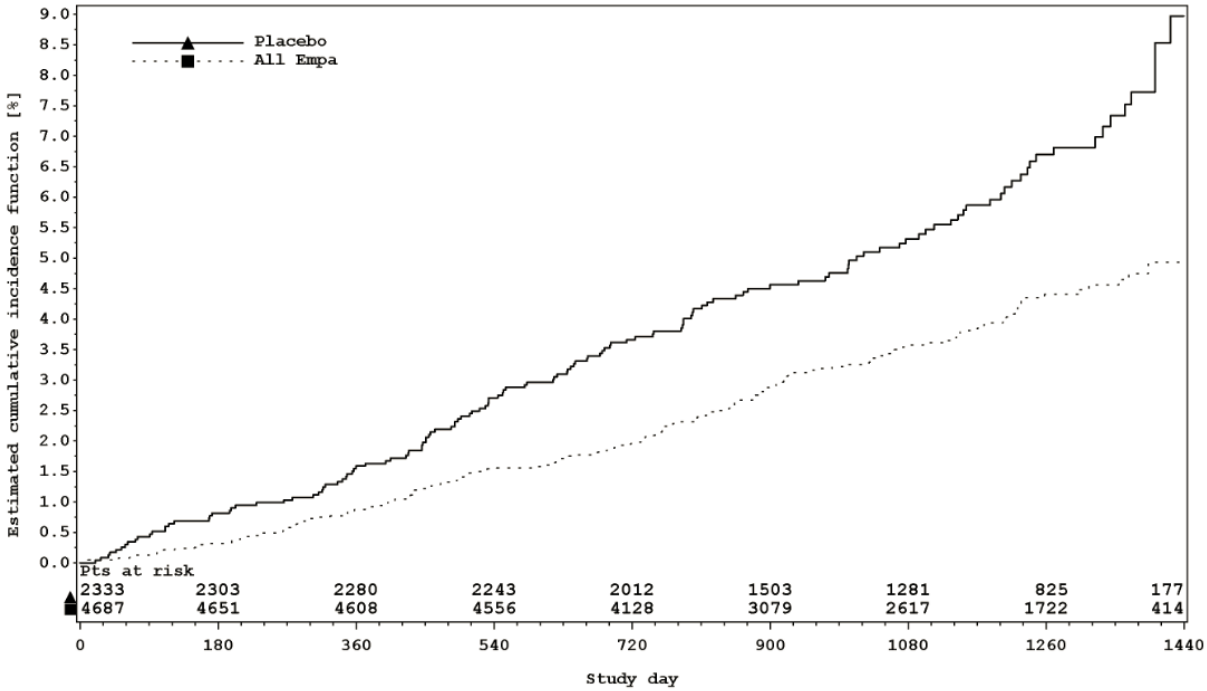
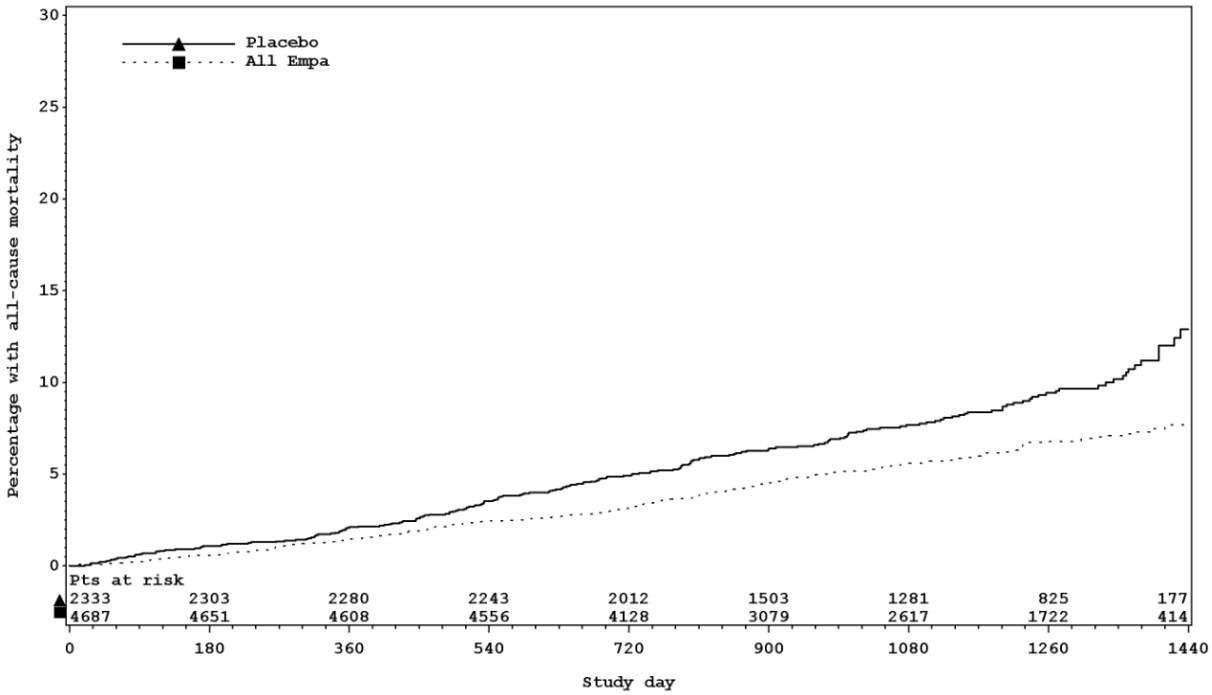


Figure 2 Time to occurrence of all-cause mortality*



*Kaplan-Meier estimate of time to all cause-mortality, pooled empagliflozin vs. placebo – treated set

Reductions in risk of heart failure requiring hospitalization or CV death

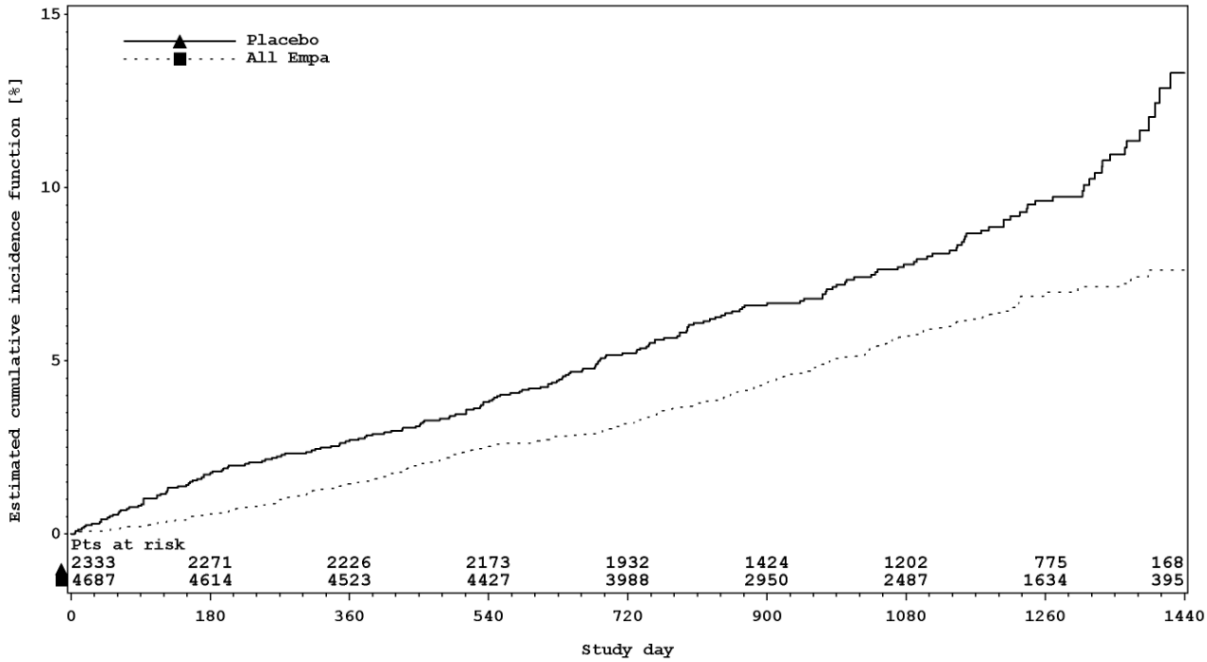
Empagliflozin is superior in reducing the risk of hospitalization for heart failure and cardiovascular death or hospitalization for heart failure compared with placebo (Table 12 and Figure 3).

Table 7 Treatment effect for hospitalization for heart failure or cardiovascular death (excluding fatal stroke) (Treated Set*)

	Placebo	**Empagliflozin** (10 and 25 mg, pooled)**
N	2333	4687
Heart failure requiring hospitalisation or CV death (excluding fatal stroke) N (%)* **	198 (8.5)	265 (5.7)
HR (95% CI)		0.66 (0.55, 0.79)
p-value		<0.0001
Heart failure requiring hospitalization N (%)	95 (4.1)	126 (2.7)
HR (95% CI)		0.65 (0.50, 0.85)
p-value		0.0017
CV death (excluding fatal stroke) N (%)	126 (5.4)	156 (3.3)
HR (95% CI)		0.61 (048, 0.77)
p-value		<0.0001

*i.e. patients who had received at least one dose of study drug
**empagliflozin 10 mg and 25 mg showed consistent results
*** time to first event

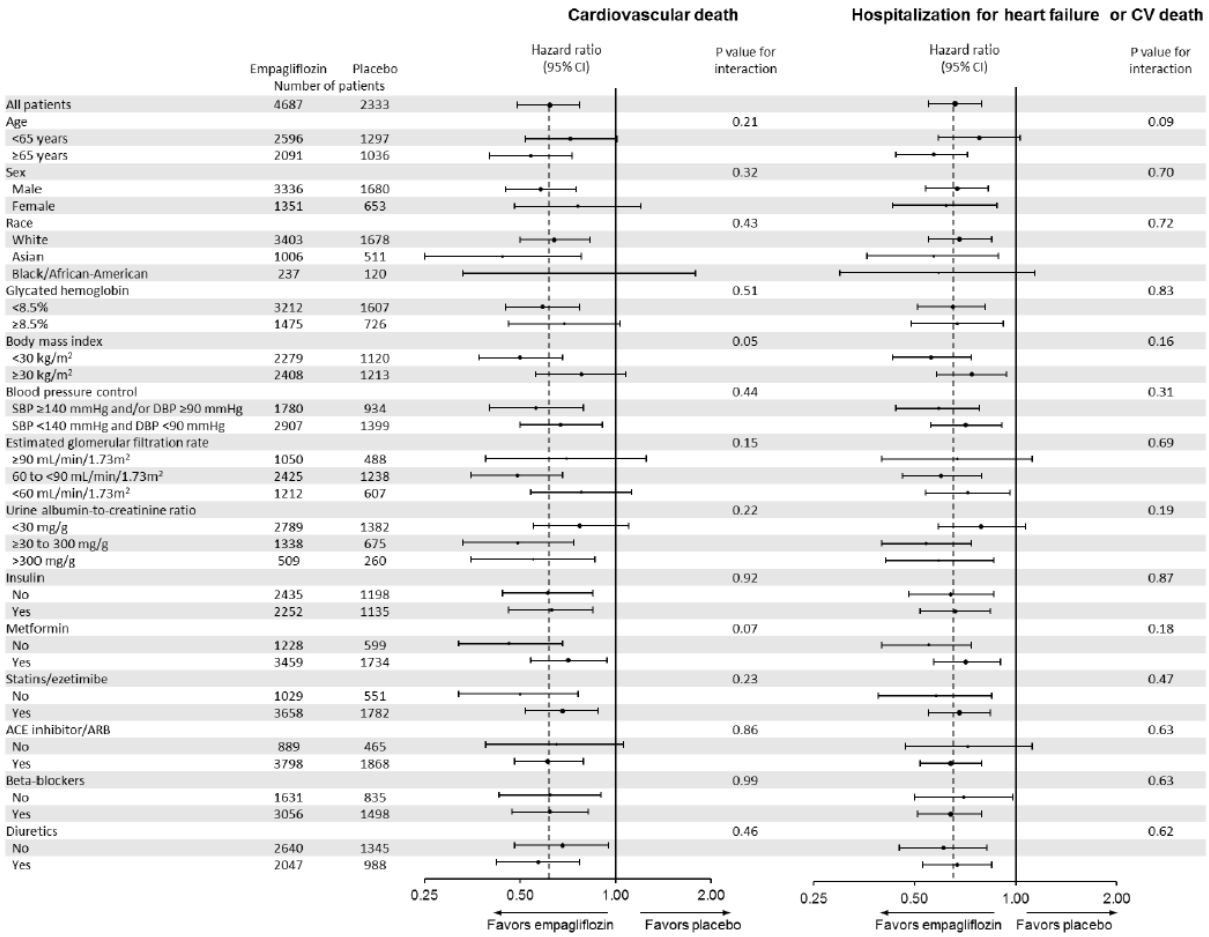
Figure 3 Time to first occurrence of first heart failure hospitalization or CV death*



*Estimated cumulative incidence function for time to first occurrence of first heart failure hospitalization or CV death, pooled empagliflozin vs placebo – treated set

The cardiovascular benefits of empagliflozin observed were consistent across the subgroups depicted in Figure 4.

Figure 4 Subgroup analyses for CV death and hospitalization for heart failure or CV death*,**



* Hospitalization for heart failure or CV death excludes fatal stroke
**p-value is for test of homogeneity of treatment group difference among subgroups (test for group by covariate interaction) with no adjustment for multiple tests and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

In the subgroup of patients who were on metformin at baseline, the effects on CV outcomes were consistent with the results observed in the entire study population of EMPA REG OUTCOME.

Diabetic kidney disease
In the EMPA-REG OUTCOME study population, the risk of new or worsening nephropathy (defined as onset of macroalbuminuria, doubling of serum creatinine, and initiation of renal replacement therapy (i.e. hemodialysis)) was significantly reduced in empagliflozin group compared to placebo (Table 13 and Figure 5).

Empagliflozin compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria (HR 1.82, 95% CI 1.40, 2.37).

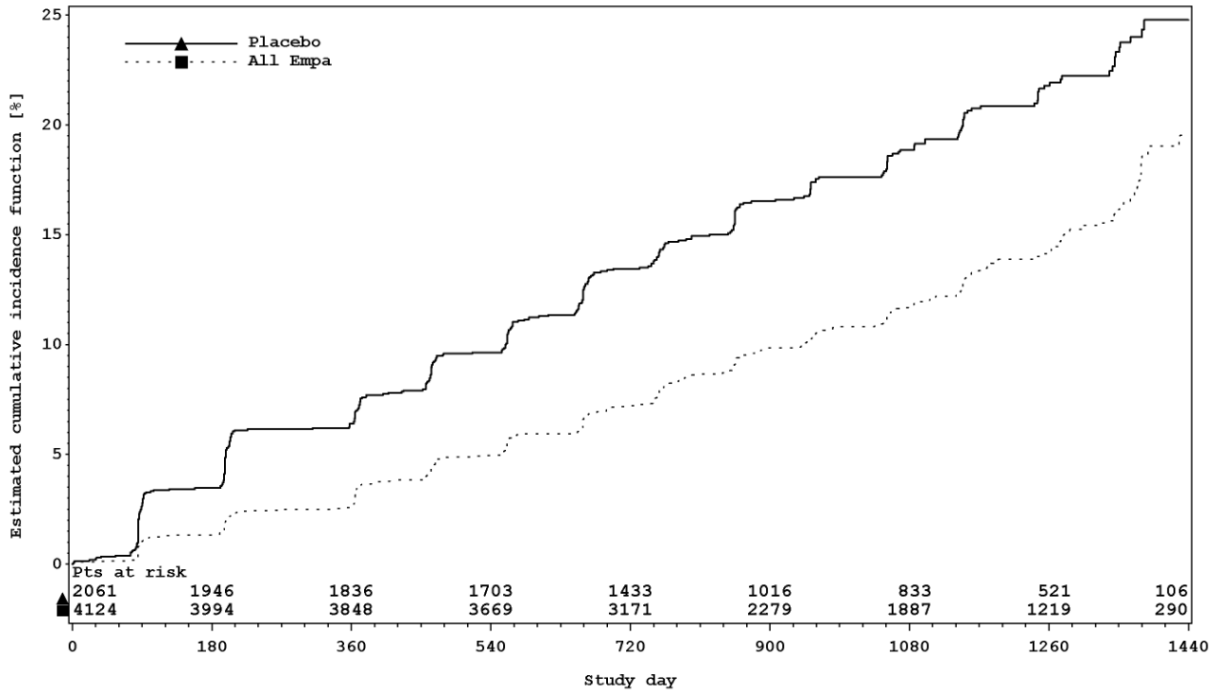
Table 8 Time to first new or worsening of nephropathy (Treated Set*)

	Placebo	**Empagliflozin (10 and 25 mg,**

		pooled)
N	2061	4124
New or worsening nephropathy N (%)	388 (18.8)	525 (12.7)
HR (95% CI)		0.61 (0.53, 0.70)
p-value		<0.0001
N	2323	4645
Doubling of serum creatinine levelN (%)**	60 (2.6)	70 (1.5)
HR (95% CI)		0.56 (0.39, 0.79
p-value		0.0009
N	2033	4091
New onset of macroalbuminuria* N (%)**	330 (16.2)	459 (11.2)
HR (95% CI)		0.62 (0.54, 0.72)
p-value		<0.0001
N	2333	4687
Initiation of continuous renal replacement therapy N (%)	14 (0.6)	13 (0.3)
HR (95% CI)		0.45 (0.21, 0.97)
p-value		0.0409
N	2333	4687
Death due to renal disease N (%)**	0	3 (0.1)

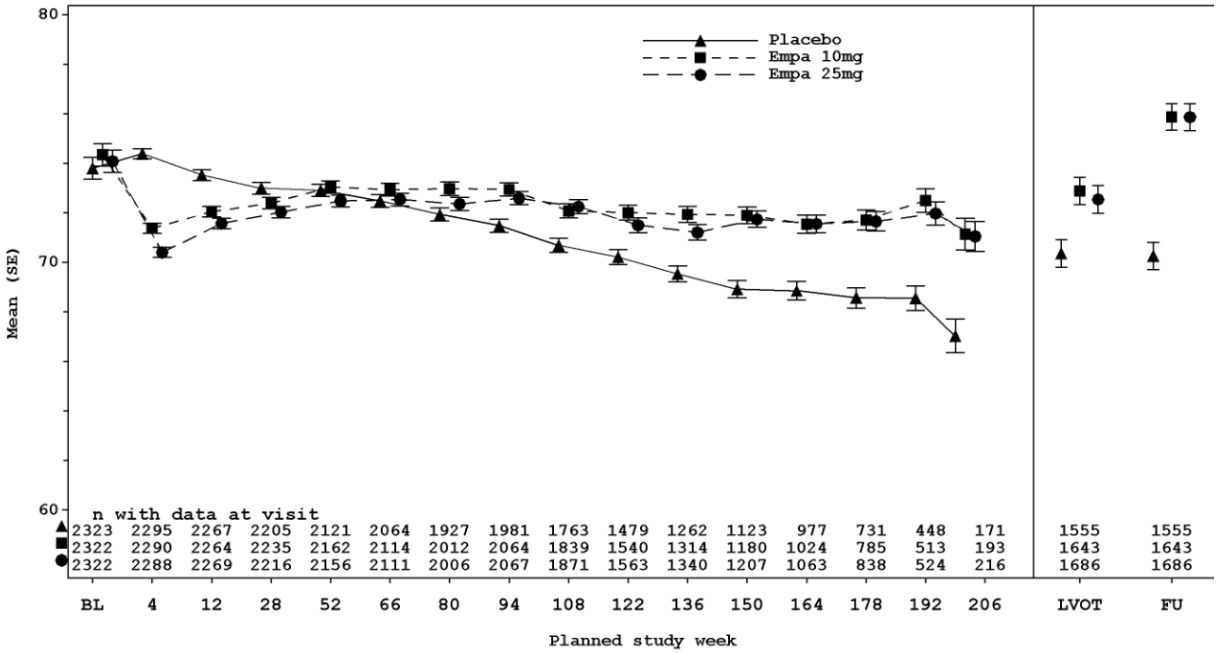
*i.e. patients who had received at least one dose of study drug
**Accompanied by an eGFR ≤45 mL/min/1.73m^2
***Urine Albumin Creatinine Ratio >300 mg/g
**** *Due to low event rate, HR not calculated

Figure 5 Time to first new or worsening of nephropathy



Treatment with empagliflozin preserved eGFR and eGFR increased during the post treatment 4-week follow up. However, the placebo group showed a gradual decline in GFR during the course of the study with no further change during 4-week follow up. (see Figure 6)

Figure 6 eGFR over time*



*eGFR (MDRD) (mL/min/1.73m^2) MMRM results over time, unadjusted last value on treatment and follow-up value - treated set – right side based on patients with available last value on treatment (LVOT) and follow-up (FU).

In the subgroup of patients who were on metformin at baseline, the effects on these renal outcomes were consistent with the results observed in the entire study population of EMPA REG OUTCOME.

Thorough QTc study

In a randomized, placebo-controlled, active-comparator, crossover study of 30 healthy subjects no increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Pharmacokinetics

Jardiance Duo
The results of bioequivalence studies in healthy subjects demonstrated that Jardiance Duo (empagliflozin/metformin hydrochloride) 5 mg/500 mg, 5 mg/850 mg, 5 mg/1000 mg, 12.5 mg/500 mg, 12.5 mg/850 mg, and 12.5 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12.5 mg empagliflozin/1000 mg metformin under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in C_{max} for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and C_{max} decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant. However, as metformin is recommended to be given with meals, Jardiance Duo is also proposed to be given with food.

The following data are findings in studies performed with empagliflozin or metformin individually.

Empagliflozin

Absorption
The pharmacokinetics of empagliflozin have been extensively characterized in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} 1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol.h/L and 259 nmol/L with empagliflozin 10 mg and 4740 nmol.h/L and 687 nmol/L with empagliflozin 25 mg once daily, respectively. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes mellitus.

The pharmacokinetics of 5 mg empagliflozin twice daily and 10 mg empagliflozin once daily were compared in healthy subjects. Overall exposure (AUCss) of empagliflozin over a 24-hour period with 5 mg administered twice daily was similar to 10 mg administered once daily. As expected, empagliflozin 5 mg administered twice daily compared with 10 mg empagliflozin once daily resulted in lower C_{max} and higher trough plasma empagliflozin concentrations (C_{min}).

Administration of 25 mg empagliflozin after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution
The apparent steady-state volume of distribution was estimated to be 73.8 L, based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism
No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases, UGT1A3, UGT1A8, UGT1A9, and UGT2B7.

Elimination
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Specific Populations

Renal Impairment
In patients with mild (eGFR: 60 - <90 mL/min/1.73 m^2), moderate (eGFR: 30 - <60 mL/min/1.73 m^2), severe (eGFR: <30 mL/min/1.73 m^2) renal impairment and patients with kidney failure/ESRD patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and

48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. In line with the Phase I study, the population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. Based on pharmacokinetics, no dosage adjustment is recommended in patients with renal insufficiency.

Hepatic Impairment
In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. Based on pharmacokinetics, no dosage adjustment is recommended in patients with hepatic impairment.

Body Mass Index (BMI)
No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Gender
No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race
No dosage adjustment is necessary based on race. Based on the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asian patients with a BMI of 25 kg/m^2 compared to non-Asian patients with a BMI of 25 kg/m^2.

Geriatric
Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Paediatric
Studies characterizing the pharmacokinetics of empagliflozin in paediatric patients have not been performed.

Metformin

Absorption
After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption are non-linear.

At the recommended metformin hydrochloride doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin hydrochloride plasma levels (C_{max}) did not exceed 5 µg/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution

Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L.

Metabolism
Metformin hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin hydrochloride is >400 mL/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma.

Special populations

Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section Dosage and administration).

Paediatric
Single dose study: After single doses of metformin 500 mg, paediatric patients, have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were approximately 33% and 40% lower, respectively, compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

TOXICOLOGY

Empagliflozin and metformin

General toxicity studies in rats up to 13 weeks were performed with the combination of empagliflozin and metformin. In a 13 week combination study with empagliflozin and metformin in rats the No-observed-adverse-effect-level (NOAEL) was based on hypochloremia seen at exposures of approximately 24- and 9-times the clinical AUC exposure of empagliflozin associated with the 10 and 25 mg doses, respectively.

An embryofetal development study in pregnant rats did not indicate a teratogenic effect attributed to the co-administration of empagliflozin and metformin at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose. At dose levels of 600 mg/kg/day, associated with 8-times the maximum recommended human dose (MRHD) of metformin in humans, teratogenicity of metformin was observed.

The following data are findings in studies performed with empagliflozin or metformin individually.

Empagliflozin

In general toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of 25 mg. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and included decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism, gluconeogenesis and electrolyte imbalances, urinary changes such as polyuria and glucosuria, and microscopic changes in kidney.

Carcinogenicity
Empagliflozin did not increase the incidence of tumours in female rats at doses up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72- and 182- times the clinical AUC exposure associated with the 25 mg and 10 mg doses, respectively. In male rats, treatment-related benign vascular proliferative lesions (hemangiomas) of the mesenteric lymph node were observed at 700 mg/kg/day, which corresponds to approximately 42- and 105-times the clinical exposure associated with the 25 mg and 10 mg doses, respectively. These tumours are common in rats and are unlikely to be relevant to humans. Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1000 mg/kg/day, which corresponds to approximately 62- and 158-times the clinical exposure associated with the 25 mg and 10 mg doses, respectively. Empagliflozin induced renal tumours in male mice at 1000 mg/kg/day, which corresponds to approximately 45- and 113-times the clinical exposure associated with the 25 mg and 10 mg doses, respectively. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

Genotoxicity
Empagliflozin is not genotoxic.

Reproduction Toxicity
Nonclinical studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic at doses up to 300 mg/kg in the rat or rabbit, which corresponds to approximately 48- and 122- times or 128- and 325- times the clinical dose of empagliflozin based on AUC exposure associated with the 25 mg and 10 mg doses, respectively. Doses of empagliflozin causing maternal toxicity in the rat also caused the malformation of bent limb bones at exposures approximately 155- and 393- times the clinical dose associated with the 25 mg and 10 mg doses, respectively. Maternally toxic doses in the rabbit also caused increased embryofetal loss at doses approximately 139- and 353- times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

In pre- and postnatal toxicity studies in rats, reduced weight gain in offspring was observed at maternal exposures approximately 4- and 11-times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period .

Metformin

Non-clinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, genotoxicity, and carcinogenic potential. In a 2 week metformin only study and 2 and 13-week toxicity empagliflozin/metformin studies in rats, metformin related toxicity was seen in heart, liver, kidneys, salivary glands, ovaries, gastrointestinal tract and adrenal glands at dosages associated with a systemic exposure of 5 times the MRHD or higher.

Metformin was not teratogenic in rats at a dose of 200 mg/kg/day associated with a systemic exposure of 4 times the MRHD (2000 mg metformin). At higher doses (500 and 1000 mg/kg/day, associated with 11 and 23 times the MRHD), teratogenicity of metformin was observed in the rat which was mostly evident as an increase in the number of skeletal malformations.

Availability :

Film coated tablet 5/500 mg
Box, 3 blisters @ 10 film coated tablet — Reg. No: DKI2056100117A1

Film coated tablet 12.5/500 mg
Box, 3 blisters @ 10 film coated tablet — Reg. No: DKI2056100117B1

Film coated tablet 12.5/850 mg
Box, 3 blisters @ 10 film coated tablet — Reg. No: DKI2056100117C1

Film coated tablet 12.5/1000mg
Box, 3 blisters @ 10 film coated tablet — Reg. No: DKI2056100117D1

Only on doctor's prescription
Harus dengan resep dokter

Product Shelf life :
See packaging for expiry date

Storage conditions :
Store below 30°C
Store in a safe place, out of the reach of children

Manufactured by :
Boehringer Ingelheim Ellas A.E.
Koropi, Greece

For :
Boehringer Ingelheim International GmbH
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