For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

EMPAZIO S 25+100 / EMPAZIO S 10+100

1. Generic Name

Empagliflozin and Sitagliptin Tablets (25 mg+100 mg) (10mg+100 mg)

2. Qualitative and quantitative Composition:

EMPAZIO S 25+100

Each film coated tablet contains:

Empagliflozin……25 mg

Sitagliptin phosphate monohydrate I.P. eq. sitagliptin …….100 mg

Excipients……. q.s.

Colours: Ferric Oxide Red USP-NF, Ferric Oxide Yellow USP-NF & Titanium Dioxide I.P.

The excipients used are Colloidal silicon dioxide, Microcrystalline cellulose PH 101, Mannitol, croscarmellose sodium, Povidone K 30, Purified water, Magnesium stearate, Polyvinyl alcohol, Polyethylene glycol 6000, talc, titanium dioxide, red iron oxide.

EMPAZIO S 10+100

Each film coated tablet contains:

Empagliflozin……10 mg

Sitagliptin phosphate monohydrate I.P. eq. sitagliptin …….100 mg

Excipients……. q.s.

Colours: Ferric Oxide Red USP-NF & Titanium Dioxide I.P.

The excipients used are Colloidal silicon dioxide, Microcrystalline cellulose PH 101, Mannitol 160C, croscarmellose sodium, Povidone K 30, Purified water, Magnesium stearate, Polyvinyl alcohol, Polyethylene glycol 6000, talc, titanium dioxide , Red iron oxide

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: Empagliflozin and Sitagliptin (25 mg+100 mg) (10mg+100 mg)

4. Clinical particulars

4.1. Therapeutic indication

EMPAZIO S is indicated in patients with Type 2 Diabetes Mellitus inadequately controlled on Metformin monotherapy.

4.2. Posology and method of administration

Posology

Dose: As directed by the Physician.

The recommended starting dose is one film-coated tablet of Empagliflozin and Sitagliptin 10 mg+ 50 mg once daily.

In patients who tolerate this starting dose and require additional glycaemic control, the dose can be increased up to one film-coated tablet of Empagliflozin and Sitagliptin 25 mg+ 100 mg once daily.

When Empagliflozin and Sitagliptin is used in combination with metformin, the metformin dose should be continued.

When Empagliflozin and Sitagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

Patients switching from empagliflozin (either 10 mg or 25 mg daily dose) and sitagliptin (either 50 or 100 mg daily dose) to fixed dose combination of Empagliflozin and Sitagliptin should receive the same daily dose of empagliflozin and sitagliptin in the fixed dose combination as in separate tablets.

Missed doses.

If a dose is missed, and it is 12 hours or more until the next dose, the dose should be taken as soon as the patient remembers. The next dose should be taken at the usual time. If a dose is missed, and it is less than 12 hours until the next dose, the dose should be skipped and the next dose should be taken at the usual time. A double dose should not be taken to compensate for a forgotten dose.

Special populations

Renal impairment

The glycaemic efficacy of empagliflozin is dependent on renal function. The glycaemic lowering efficacy of empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe 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.

If no adequate strength of fixed dose combination of Empagliflozin, and Sitagliptin is available, individual monocomponents should be used instead of the fixed-dose combination as per below table.

Table 1: Posology of individual active substance for renal impaired patients

GFR mL/min	**Empagliflozin**	**Sitagliptin**
60-89	Initiate with 10 mg. In patients tolerating 10 mg and requiring additional glycaemic control, the dose can be increased to 25 mg	Maximum daily dose is 100 mg
45-59	Initiate with 10 mg.[a] Continue with 10 mg in patients already taking empagliflozin.	Maximum daily dose is 100 mg.
30-44	Initiate with 10 mg.[a] Continue with 10 mg in patients already taking empagliflozin.b	Maximum daily dose is 50 mg

< 30	Empagliflozin is not recommended	Maximum daily dose is 25 mg.

[a] patient with type 2 diabetes mellitus and established cardiovascular disease.

Empagliflozin, and Sitagliptin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis, as there are insufficient data on empagliflozin to support use in these patients.

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment and therapeutic experience in such patients is limited. Therefore, Empagliflozin, and Sitagliptin is not recommended for use in this population.

Elderly

No dose adjustment based on age is required. However, renal function and risk of volume depletion should be considered in patients 75 years and older.

Paediatric population

Safety and efficacy in paediatric patients below 18 years of age have not been established. No data are available.

Method of administration

Empagliflozin, and Sitagliptin tablets are for oral use and can be taken with or without a meal at any time of the day at regular intervals. The tablets should be swallowed whole with water.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4. Special warnings and precautions for use

Ketoacidosis

Cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl). It is not known if ketoacidosis is more likely to occur with higher doses of empagliflozin. Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients.

The risk of 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.

In patients where ketoacidosis is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of ketoacidosis include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous ketoacidosis while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Empagliflozin, and Sitagliptin should not be used in patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased ketoacidosis occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.

Renal impairment

In patients with an eGFR below 60 mL/min/1.73 m2 the daily dose of empagliflozin is limited to 10 mg. Empagliflozin Sitagliptin is not recommended when eGFR is below 30 mL/min/1.73 m2. Empagliflozin/Sitagliptin should not be used in patients with ESRD or in patients on dialysis. There are insufficient data to support use in these patients.

Monitoring of renal function

Assessment of renal function is recommended as follows:

- Prior to empagliflozin + Sitagliptin initiation and periodically during treatment, i.e. at least yearly.
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

Hepatic injury

Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established

Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment.

Chronic kidney disease

Patients with albuminuria may benefit more from treatment with empagliflozin.

Chronic kidney disease

There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease (eGFR ≥30 mL/min/1.73 m2) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin.

Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying 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 empagliflozin + Sitagliptin should be considered until the fluid loss is corrected.

Elderly

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).

Complicated urinary tract infections

Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of empagliflozin + Sitagliptin should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients with diabetes mellitus taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Empagliflozin and Sitagliptin should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

Urine laboratory assessments

Due to the mechanism of action of empagliflozin, patients taking Empagliflozin and Sitagliptin will test positive for glucose in their urine.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis.

Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported.

If pancreatitis is suspected, Empagliflozin and Sitagliptin should be discontinued; if acute pancreatitis is confirmed, Sitagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products

Empagliflozin and Sitagliptin as single agents showed an incidence of hypoglycaemia comparable to placebo when used alone or in combination with other antidiabetics not known to cause hypoglycaemia (e.g. metformin, thiazolidinediones). When used in combination with antidiabetics known to cause hypoglycaemia (e.g. sulphonylureas and/or insulin), the incidence of hypoglycaemia of both agents was increased.

There are no data about the hypoglycaemic risk of Empagliflozin and Sitagliptin when used with insulin and/or sulphonylurea. However, caution is advised when Empagliflozin and Sitagliptin is used in combination with antidiabetics. A dose reduction of the sulphonylurea or insulin may be considered. .

Hypersensitivity reactions

Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, Empagliflozin and Sitagliptin should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted.

Bullous pemphigoid

There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, Empagliflozin and Sitagliptin should be discontinued.

4.5. Drugs interactions

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 and insulin secretagogues

Insulin and 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 and Sitagliptin.

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

Empagliflozin is mainly excreted unchanged. A minor fraction is metabolised via uridine 5'-diphosphoglucuronosyltransferases (UGT); therefore, a clinically relevant effect of UGT

inhibitors on empagliflozin is not expected. The effect of UGT induction on empagliflozin (e.g. induction by rifampicin or phenytoin) has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy of empagliflozin. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Empagliflozin and Sitagliptin is appropriate.

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations (C_{max}) and a 53% increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C_{max} increased by 15% and AUC increased by 59% following co-administration. These changes were not considered to be clinically meaningful.

Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in C_{max} and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Effects of empagliflozin on other medicinal products

Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

Effects of other medicinal products on sitagliptin

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

In reported vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study. In reported vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited in vitro by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated in vivo.

- *Metformin*: Co-administration of multiple twice-daily doses of 1,000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

- *Ciclosporin*: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on other medicinal products

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

In reported vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein in vivo.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are no data from the use of Empagliflozin and Sitagliptin 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. As a precautionary measure, it is preferable to avoid the use of Empagliflozin and Sitagliptin during pregnancy.

Breast-feeding

No data in humans are available on excretion of Empagliflozin and Sitagliptin into milk. Available toxicological data in animals have shown excretion of Empagliflozin and Sitagliptin in milk. A risk to the newborns/infants cannot be excluded. Empagliflozin and Sitagliptin should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for Empagliflozin and Sitagliptin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Special Population:

Elderly

No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account..

Paediatric population

The safety and efficacy of Empagliflozin and Sitagliptin in children and adolescents has not yet been established. No data are available.

4.7. Effects on ability to drive and use machines

Empagliflozin and Sitagliptin has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Empagliflozin and Sitagliptin is used in combination with a sulphonylurea and/or insulin.

4.8. Undesirable effects

Summary of the safety profile

Empagliflozin

Type 2 diabetes mellitus

A total of 15 582 patients with type 2 diabetes were included in clinical studies to evaluate the safety of empagliflozin, of which 10 004 patients received empagliflozin, either alone or in combination with metformin, a sulphonylurea, pioglitazone, DPP-4 inhibitors, or insulin.

In 6 placebo-controlled trials of 18 to 24 weeks duration, 3 534 patients were included of which 1 183 were treated with placebo and 2 351 with empagliflozin. The overall incidence of adverse events in patients treated with empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycaemia when used with sulphonylurea or insulin (see description of selected adverse reactions).

Heart failure

The EMPEROR studies included patients with heart failure and either reduced ejection fraction (N=3 726) or preserved ejection fraction (N=5 985) treated with empagliflozin 10 mg or placebo. Approximately half of the patients had type 2 diabetes mellitus. The most frequent adverse reaction of the pooled EMPEROR-Reduced and EMPEROR-Preserved studies was volume depletion (empagliflozin 10 mg: 11.4%. placebo: 9.7%).

Chronic kidney disease

The EMPA-KIDNEY study included patients with chronic kidney disease (N = 6 609) treated with 10 mg empagliflozin or placebo. About 44% of the patients had type 2 diabetes mellitus. The most frequent adverse events in the EMPA-KIDNEY study were gout (empagliflozin 7.0% vs placebo 8.0%), and acute kidney injury (empagliflozin 2.8% vs placebo 3.5%) which were more frequently reported in patients on placebo.

The overall safety profile of empagliflozin was generally consistent across the studied indications.

Tabulated list of adverse reactions

Empagliflozin

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received empagliflozin in placebo-controlled studies are presented in the table below.

The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), or very rare (<1/10 000), and not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled studies and from post-marketing experience

System organ class	Very common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[a] Urinary tract infection (including pyelonephritis and urosepsis)[a]		Necrotising fasciitis of the perineum (Fournier's gangrene)*	
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[a]	Thirst	Ketoacidosis*		
Gastrointestinal disorders		Constipation			
Skin and subcutaneous tissue disorders		Pruritus (generalised) Rash	Urticaria Angioedema		
Vascular disorders	Volume depletion[a]				
Renal and urinary disorders		Increased urination[a]	Dysuria		Tubulo-interstitial nephritis
Investigations		Serum lipids increased[a]	Blood creatinine increased/ Glomerular filtration rate decreased[a] Haematocrit increased[a]		

a: see subsections below for additional information

* see section 4.4

Description of selected adverse reactions

Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as monotherapy, add-on to metformin, add-on to pioglitazone with or without metformin, as add-on to linagliptin and metformin, and as adjunct to standard care therapy and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to metformin and a sulphonylurea (empagliflozin 10 mg: 16.1%, empagliflozin 25 mg: 11.5%, placebo: 8.4%), add-on to basal insulin with or without metformin and with or without a sulphonylurea (empagliflozin 10 mg: 19.5%, empagliflozin 25 mg: 28.4%, placebo: 20.6% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg and 25 mg: 36.1%, placebo 35.3% over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 39.8%, empagliflozin 25 mg: 41.3%, placebo:

37.2% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 51.1%, empagliflozin 25 mg: 57.7%, placebo: 58% over the 52-week trial).

In the EMPEROR heart failure studies, similar frequency of hypoglycaemia was noted when used add-on to sulphonylurea or insulin (empagliflozin 10 mg: 6.5%, placebo: 6.7%).

Major hypoglycaemia (events requiring assistance)

No increase in major hypoglycaemia was observed with empagliflozin compared to placebo as monotherapy, add-on to metformin, add-on to metformin and a sulphonylurea, add-on to pioglitazone with or without metformin, add-on to linagliptin and metformin, as adjunct to standard care therapy and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to basal insulin with or without metformin and with or without a sulphonylurea (empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo: 0% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo 0% over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 0.5%, empagliflozin 25 mg: 0.5%, placebo: 0.5% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 1.6%, empagliflozin 25 mg: 0.5%, placebo: 1.6% over the 52-week trial).

In the EMPEROR heart failure studies, major hypoglycaemia was observed at similar frequencies in patients with diabetes mellitus when treated with empagliflozin and placebo as add-on to sulphonylurea or insulin (empagliflozin 10 mg: 2.2%, placebo: 1.9%).

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in patients treated with empagliflozin (empagliflozin 10 mg: 4.0%, empagliflozin 25 mg: 3.9%) compared to placebo (1.0%). These infections were reported more frequently in females treated with empagliflozin compared to placebo, and the difference in frequency was less pronounced in males. The genital tract infections were mild or moderate in intensity.

In the EMPEROR heart failure studies, the frequency of these infections was more pronounced in patients with diabetes mellitus (empagliflozin 10 mg: 2.3%; placebo: 0.8%) than in patients without diabetes mellitus (empagliflozin 10 mg: 1.7%; placebo: 0.7%) when treated with empagliflozin compared to placebo.

Increased urination

Increased urination (including the predefined terms pollakiuria, polyuria, and nocturia) was observed at higher frequencies in patients treated with empagliflozin (empagliflozin 10 mg:

3.5%, empagliflozin 25 mg: 3.3%) compared to placebo (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was similar for placebo and empagliflozin (<1%).

In the EMPEROR heart failure studies, increased urination was observed at similar frequencies in patients treated with empagliflozin and placebo (empagliflozin 10 mg: 0.9%, placebo 0.5%).

Urinary tract infection

The overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo (7.0% and 7.2%) and higher in empagliflozin 10 mg (8.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity (mild, moderate, severe) of urinary tract infection was similar in patients treated with empagliflozin and placebo. Urinary tract infection was reported more frequently in females treated with empagliflozin compared to placebo; there was no difference in males.

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 similar in patients treated with empagliflozin (empagliflozin 10 mg: 0.6%, empagliflozin 25 mg: 0.4%) and placebo (0.3%). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2.3%) or empagliflozin 25 mg (4.3%) compared to placebo (2.1%).

Blood creatinine increased/Glomerular filtration rate decreased

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%). Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with empagliflozin were generally transient during continuous treatment or reversible after drug discontinuation of treatment.

Consistently, in the EMPA-REG OUTCOME study, patients treated with empagliflozin experienced an initial fall in eGFR (mean: 3 ml/min/1.73 m^2). Thereafter, eGFR was maintained during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting acute haemodynamic changes may play a role in these renal function changes. This phenomenon is also observed in the EMPEROR heart failure studies and the EMPA-KIDNEY study.

Serum lipids increased

Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 4.9% and 5.7% versus 3.5%; HDL-cholesterol 3.3% and 3.6% versus 0.4 %; LDL-cholesterol 9.5% and 10.0% versus 7.5%; triglycerides 9.2% and

9.9% versus 10.5%.

Haematocrit increased

Mean changes from baseline in haematocrit were 3.4% and 3.6% for empagliflozin 10 mg and 25 mg, respectively, compared to 0.1% 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.

Sitagliptin

Tabulated list of adverse reactions

Adverse reactions are listed below in table by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 3 The frequency of adverse reactions identified from reported placebo-controlled clinical studies of Sitagliptin monotherapy and post-marketing experience

Adverse reaction	**Frequency of adverse reaction**
Blood and lymphatic system disorders	
thrombocytopenia	Rare
Immune system disorders	
hypersensitivity reactions including anaphylactic responses	Frequency not known
Metabolism and nutrition disorders	
hypoglycaemia	Common
Nervous system disorders	
headache	Common
dizziness	Uncommon
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease	Frequency not known
Gastrointestinal disorders	
constipation	Uncommon
vomiting	Frequency not known
acute pancreatitis	Frequency not known

fatal and non-fatal haemorrhagic and necrotizing pancreatitis	Frequency not known
Skin and subcutaneous tissue disorders	
pruritus	Uncommon
angioedema	Frequency not known
rash	Frequency not known
urticaria	Frequency not known
cutaneous vasculitis	Frequency not known
exfoliative skin conditions including Stevens-Johnson syndrome	Frequency not known
bullous pemphigoid	Frequency not known
Musculoskeletal and connective tissue disorders	
arthralgia	Frequency not known
myalgia	Frequency not known
pain in extremity	Frequency not known
back pain	Frequency not known
arthropathy	Frequency not known
Renal and urinary disorders	
impaired renal function	Frequency not known
acute renal failure	Frequency not known

Adverse reactions were identified through post-marketing surveillance.

Description of selected adverse reactions:

In addition to the drug-related adverse experiences described above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5 % and more commonly in patients treated with sitagliptin included upper respiratory tract infection and nasopharyngitis. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with sitagliptin (not reaching the

5 % level, but occurring with an incidence of > 0.5 % higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other anti-diabetic medicinal products than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequency very common with the combination of sulphonylurea and metformin), influenza (common with insulin (with or without metformin)), nausea and vomiting (common with metformin), flatulence (common with metformin or pioglitazone), constipation (common with the combination of sulphonylurea and metformin), peripheral oedema (common with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (uncommon with metformin), and dry mouth (uncommon with insulin (with or without metformin)).

Paediatric population

In clinical trials with sitagliptin in paediatric patients with type 2 diabetes mellitus aged 10 to17 years, the profile of adverse reactions was comparable to that observed in adults.

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7 % in sitagliptin-treated patients and 2.5 % in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0 % in sitagliptin-treated patients and 0.7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3 % in sitagliptin-treated patients and 0.2 % in placebo-treated patients.

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Symptoms

In controlled clinical studies single doses of up to 800 mg empagliflozin in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg in humans.

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical

adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

Treatment

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

The removal of empagliflozin by haemodialysis has not been studied. Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

5. Pharmacological properties

5.1. Mechanism of Action

Empagliflozin and Sitagliptin tablets combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and sitagliptin, DPP-4 inhibitor.

Empagliflozin

Empagliflozin is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

In patients with type 2 diabetes, 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 the 4-week treatment period, averaging approximately 78 g/day. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

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-β (HOMA-β) was 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 diuresis which may contribute to sustained and moderate reduction of blood pressure.

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to: increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart, downregulating of sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodeling, filling pressures and diastolic function as well as preserving kidney structure and function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial cardiac and renal effects.

Sitagliptin

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

In a reported two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

5.2. Pharmacodynamic properties

Empagliflozin

Clinical efficacy and safety

Type 2 diabetes mellitus

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

Glycaemic efficacy and cardiovascular outcomes have been assessed in a total of 14 663 patients with type 2 diabetes who were treated in 12 double-blind, placebo- and active-controlled clinical studies, of which 9 295 received empagliflozin (empagliflozin 10 mg: 4 165 patients; empagliflozin 25 mg: 5 130 patients). Five studies had treatment durations of 24 weeks; extensions of those and other studies had patients exposed to empagliflozin for up to 102 weeks.

Treatment with empagliflozin as monotherapy and in combination with metformin, pioglitazone, a sulphonylurea, DPP-4 inhibitors, and insulin lead to clinically relevant improvements in HbA1c, fasting plasma glucose (FPG), body weight, and systolic and diastolic blood pressure. Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA1c goal of less than 7% and fewer patients needing glycaemic rescue

compared to empagliflozin 10 mg and placebo. Higher baseline HbA1c was associated with a greater reduction in HbA1c. In addition, empagliflozin as adjunct to standard care therapy reduced cardiovascular mortality in patients with type 2 diabetes and established cardiovascular disease.

Monotherapy

The efficacy and safety of empagliflozin as monotherapy was evaluated in a double-blind, placebo- and active-controlled study of 24 weeks duration in treatment-naïve patients. Treatment with empagliflozin resulted in a statistically significant ($p<0.0001$) reduction in HbA1c compared to placebo and a clinically meaningful decrease in FPG. In a pre-specified analysis of patients (N=201) with a baseline HbA1c ≥8.5%, treatment resulted in a reduction in HbA1c from baseline of -1.44% for empagliflozin 10 mg, -1.43% for empagliflozin 25 mg, -1.04% for sitagliptin, and an increase of 0.01% for placebo. In the double-blind placebo-controlled extension of this study, reductions of HbA1c, body weight and blood pressure were sustained up to Week 76.

Table 4: Efficacy results of a 24 week placebo-controlled study of empagliflozin as monotherapy[a]

	Placebo	**Empagliflozin**		**Sitagliptin**
		10 mg	**25 mg**	**100 mg**
N	228	224	224	223
HbA1c (%)				
Baseline (mean)	7.91	7.87	7.86	7.85
Change from baseline[1]	0.08	-0.66	-0.78	-0.66
Difference from placebo[1] (97.5% CI)		-0.74* (-0.90, -0.57)	-0.85* (-1.01, -0.69)	-0.73 (-0.88, -0.59)[3]
N	208	204	202	200
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	12.0	35.3	43.6	37.5
N	228	224	224	223
Body Weight (kg)				
Baseline (mean)	78.23	78.35	77.80	79.31
Change from baseline[1]	-0.33	-2.26	-2.48	0.18
Difference from placebo[1] (97.5% CI)		-1.93* (-2.48, -1.38)	-2.15* (-2.70,-1.60)	0.52 (-0.04, 1.00)[3]
N	228	224	224	223
SBP (mmHg)[4]				
Baseline (mean)	130.4	133.0	129.9	132.5
Change from baseline[1]	-0.3	-2.9	-3.7	0.5

Difference from placebo[1] (97.5% CI)		-2.6* (-5.2, -0.0)	-3.4* (-6.0, -0.9)	0.8 (-1.4, 3.1)[3]

[a.] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

1. Mean adjusted for baseline value
2. Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
3. 95% CI
4. LOCF, values after antihypertensive rescue censored

*p-value <0.0001

Combination therapy

Empagliflozin as add-on to metformin, sulphonylurea, pioglitazone

Empagliflozin as add-on to metformin, metformin and a sulphonylurea, or pioglitazone with or without metformin resulted in statistically significant (p<0.0001) reductions in HbA1c and body weight compared to placebo. In addition it resulted in a clinically meaningful reduction in FPG, systolic and diastolic blood pressure compared to placebo.

In the double-blind placebo-controlled extension of these studies, reduction of HbA1c, body weight and blood pressure were sustained up to Week 76.

Table 5: Efficacy results of 24 week placebo-controlled studies[a]

Add-on to metformin therapy			
	Placebo	**Empagliflozin**	
		10 mg	**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	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
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)
Add-on to metformin and a sulphonylurea therapy			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	225	225	216
HbA1c (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.17	-0.82	-0.77
Difference from placebo[1] (97.5% CI)		-0.64* (-0.79, -0.49)	-0.59* (-0.74, -0.44)
N	216	209	202
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	9.3	26.3	32.2
N	225	225	216
Body Weight (kg)			
Baseline (mean)	76.23	77.08	77.50
Change from baseline[1]	-0.39	-2.16	-2.39
Difference from placebo[1] (97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)
N	225	225	216
SBP (mmHg)[2]			
Baseline (mean)	128.8	128.7	129.3
Change from baseline[1]	-1.4	-4.1	-3.5
Difference from placebo[1] (95% CI)		-2.7 (-4.6, -0.8)	-2.1 (-4.0, -0.2)
Add-on to pioglitazone +/- metformin therapy			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	165	165	168
HbA1c (%)			
Baseline (mean)	8.16	8.07	8.06
Change from baseline[1]	-0.11	-0.59	-0.72
Difference from placebo[1] (97.5% CI)		-0.48* (-0.69, -0.27)	-0.61* (-0.82, -0.40)
N	155	151	160
Patients (%) achieving HbA1c <7% with baseline	7.7	24	30

HbA1c ≥7%[2]			
N	165	165	168
Body Weight (kg)			
Baseline (mean)	78.1	77.97	78.93
Change from baseline[1]	0.34	-1.62	-1.47
Difference from placebo[1] (97.5% CI)		-1.95* (-2.64, -1.27)	-1.81* (-2.49, -1.13)
N	165	165	168
SBP (mmHg)[3]			
Baseline (mean)	125.7	126.5	126
Change from baseline[1]	0.7	-3.1	-4.0
Difference from placebo[1] (95% CI)		-3.9 (-6.23, -1.50)	-4.7 (-7.08, -2.37)

a. Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

1 Mean adjusted for baseline value

2 Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure

3 LOCF, values after antihypertensive rescue censored

* p-value <0.0001

In combination with metformin in drug-naïve patients

A factorial design study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in drug-naïve patients. Treatment with empagliflozin in combination with metformin (5 mg and 500 mg; 5 mg and 1 000 mg; 12.5 mg and 500 mg, and 12.5 mg and 1 000 mg given twice daily) provided statistically significant improvements in HbA1c and led to greater reductions in FPG (compared to the individual components) and body weight (compared to metformin).

Table 6: Efficacy results at 24 week comparing empagliflozin in combination with metformin to the individual components[a]

	Empagliflozin 10 mg[b]			Empagliflozin 25 mg[b]			Metformin[c]	
	+ Met 1 000 mg[c]	+ Met 2 000 mg[c]	No Met	+ Met 1 000 mg[c]	+ Met 2 000 mg[c]	No Met	1 000 mg	2 000 mg
N	161	167	169	165	169	163	167	162
HbA1c (%)								
Baseline (mean)	8.68	8.65	8.62	8.84	8.66	8.86	8.69	8.55

Change from baseline[1]	-1.98	-2.07	-1.35	-1.93	-2.08	-1.36	-1.18	-1.75
Comparison vs. empa (95% CI)[1]	-0.63* (-0.86, -0.40)	-0.72* (-0.96, -0.49)		-0.57* (-0.81, -0.34)	-0.72* (-0.95, -0.48)			
Comparison vs. met (95% CI)[1]	-0.79* (-1.03, -0.56)	-0.33* (-0.56, -0.09)		-0.75* (-0.98 - 0.51)	-0.33* (-0.56, -0.10)			

Met = metformin; empa = empagliflozin

1. mean adjusted for baseline value
a. Analyses were performed on the full analysis set (FAS) using an observed cases (OC) approach
b. Given in two equally divided doses per day when given together with metformin
c. Given in two equally divided doses per day

*p≤0.0062 for HbA1c

Empagliflozin in patients inadequately controlled with metformin and linagliptin

In patients inadequately controlled with metformin and linagliptin 5 mg, treatment with both empagliflozin 10 mg or 25 mg resulted in statistically significant (p<0.0001) reductions in HbA1c and body weight compared to placebo. In addition it resulted in clinically meaningful reductions in FPG, systolic and diastolic blood pressure compared to placebo.

Table 7: Efficacy results of a 24 week placebo-controlled study in patients inadequately controlled with metformin and linagliptin 5 mg

Add-on to metformin and linagliptin 5 mg			
	Placebo[5]	**Empagliflozin[6]**	
		10 mg	**25 mg**
N	106	109	110
HbA1c (%)[3]			
Baseline (mean)	7.96	7.97	7.97
Change from baseline[1]	0.14	-0.65	-0.56
Difference from placebo (95% CI)		-0.79* (-1.02, -0.55)	-0.70* (-0.93, -0.46)
N	100	100	107
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	17.0	37.0	32.7
N	106	109	110
Body Weight (kg)[3]			
Baseline (mean)	82.3	88.4	84.4
Change from baseline[1]	-0.3	-3.1	-2.5

Difference from placebo (95% CI)		-2.8* (-3.5, -2.1)	-2.2* (-2.9, -1.5)
N	106	109	110
SBP (mmHg)[4]			
Baseline (mean)	130.1	130.4	131.0
Change from baseline[1]	-1.7	-3.0	-4.3
Difference from placebo (95% CI)		-1.3 (-4.2, 1.7)	-2.6 (-5.5, 0.4)

1. Mean adjusted for baseline value
2. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
3. MMRM model on FAS (OC) included baseline HbA1c, baseline eGFR (MDRD), geographical region, visit, treatment, and treatment by visit interaction. For weight, baseline weight was included.
4. MMRM model included baseline SBP and baseline HbA1c as linear covariate(s), and baseline eGFR, geographical region, treatment, visit, and visit by treatment interaction as fixed effects.
5. Patients randomised to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin
6. Patients randomised to the empagliflozin 10 mg or 25 mg groups were receiving empagliflozin 10 mg or 25 mg and linagliptin 5 mg with background metformin * p-value <0.0001

In a pre-specified subgroup of patients with baseline HbA1c greater or equal than 8.5% the reduction from baseline in HbA1c was -1.3% with empagliflozin 10 mg or 25 mg at 24 weeks (p<0.0001) compared to placebo.

Empagliflozin 24 months data, as add-on to metformin in comparison to glimepiride

In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (up to 4 mg per day) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA1c, and a clinically meaningful reduction in FPG, compared to glimepiride. Empagliflozin daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure and a statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride, p<0.0001).

Table 8: Efficacy results at 104 week in an active controlled study comparing empagliflozin to glimepiride as add-on to metformin[a]

	Empagliflozin 25 mg	**Glimepiride[b]**
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	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
SBP (mmHg)[2]		
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)	

a. Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy
b. Up to 4 mg glimepiride
1. Mean adjusted for baseline value
2. LOCF, values after antihypertensive rescue censored

* p-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority

** p-value <0.0001

Add-on to insulin therapy

Empagliflozin as add-on to multiple daily insulin

The efficacy and safety of empagliflozin as add-on to multiple daily insulin with or without concomitant metformin therapy was evaluated in a double-blind, placebo-controlled trial of 52 weeks duration. During the initial 18 weeks and the last 12 weeks, the insulin dose was kept stable, but was adjusted to achieve pre-prandial glucose levels <100 mg/dl [5.5 mmol/l], and post-prandial glucose levels <140 mg/dl [7.8 mmol/l] between Weeks 19 and 40. At Week 18, empagliflozin provided statistically significant improvement in HbA1c compared with placebo.

At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared with placebo and a reduction in FPG and body weight.

Table 9: Efficacy results at 18 and 52 weeks in a placebo-controlled study of empagliflozin as add on to multiple daily doses of insulin with or without metformin

	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	188	186	189
HbA1c (%) at week 18			
Baseline (mean)	8.33	8.39	8.29

Change from baseline[1]	-0.50	-0.94	-1.02
Difference from placebo[1] (97.5% CI)		-0.44* (-0.61, -0.27)	-0.52* (-0.69, -0.35)
N	115	119	118
HbA1c (%) at week 52[2]			
Baseline (mean)	8.25	8.40	8.37
Change from baseline[1]	-0.81	-1.18	-1.27
Difference from placebo[1] (97.5% CI)		-0.38*** (-0.62, -0.13)	-0.46* (-0.70, -0.22)
N	113	118	118
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7% at week 52	26.5	39.8	45.8
N	115	118	117
Insulin dose (IU/day) at week 52[2]			
Baseline (mean)	89.94	88.57	90.38
Change from baseline[1]	10.16	1.33	-1.06
Difference from placebo[1] (97.5% CI)		-8.83# (-15.69, -1.97)	-11.22** (-18.09, -4.36)
N	115	119	118
Body Weight (kg) at week 52[2]			
Baseline (mean)	96.34	96.47	95.37
Change from baseline[1]	0.44	-1.95	-2.04
Difference from placebo[1] (97.5% CI)		-2.39* (-3.54, -1.24)	-2.48* (-3.63, -1.33)

1 Mean adjusted for baseline value

2 Week 19-40: treat-to-target regimen for insulin dose adjustment to achieve predefined glucose target levels (pre-prandial <100 mg/dl (5.5 mmol/l), post-prandial <140 mg/dl (7.8 mmol/l)

* p-value <0.0001

** p-value = 0.0003

*** p-value = 0.0005

p-value = 0.0040

Empagliflozin as add-on to basal insulin

The efficacy and safety of empagliflozin as add-on to basal insulin with or without metformin and/or a sulphonylurea was evaluated in a double-blind, placebo-controlled trial of 78 weeks

duration. During the initial 18 weeks the insulin dose was kept stable, but was adjusted to achieve a FPG <110 mg/dl in the following 60 weeks.

At week 18, empagliflozin provided statistically significant improvement in HbA1c. At 78 weeks, empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared to placebo. Furthermore, empagliflozin resulted in a reduction in FPG, body weight, and blood pressure.

Table 10: Efficacy results at 18 and 78 weeks in a placebo-controlled study of empagliflozin as add-on to basal insulin with or without metformin or a sulphonylurea[a]

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	125	132	117
HbA1c (%) at week 18			
Baseline (mean)	8.10	8.26	8.34
Change from baseline[1]	-0.01	-0.57	-0.71
Difference from placebo[1] (97.5% CI)		-0.56* (-0.78, -0.33)	-0.70* (-0.93, -0.47)
N	112	127	110
HbA1c (%) at week 78			
Baseline (mean)	8.09	8.27	8.29
Change from baseline[1]	-0.02	-0.48	-0.64
Difference from placebo[1] (97.5% CI)		-0.46* (-0.73, -0.19)	-0.62* (-0.90, -0.34)
N	112	127	110
Basal insulin dose (IU/day) at week 78			
Baseline (mean)	47.84	45.13	48.43
Change from baseline[1]	5.45	-1.21	-0.47
Difference from placebo[1] (97.5% CI)		-6.66** (-11.56, -1.77)	-5.92** (-11.00, -0.85)

a. Full analysis set (FAS) - Completers using last observation carried forward (LOCF) prior to glycaemic rescue therapy

1. mean adjusted for baseline value

* p-value <0.0001

** p-value <0.025

Patients with renal impairment, 52 week placebo controlled data

The efficacy and safety of empagliflozin as add-on to antidiabetic therapy was evaluated in patients with renal impairment in a double-blind, placebo-controlled study for 52 weeks. Treatment with empagliflozin led to a statistically significant reduction of HbA1c and clinically meaningful improvement in FPG compared to placebo at Week 24. The improvement in HbA1c, body weight, and blood pressure was sustained up to 52 weeks.

Table 11: Results at 24 week in a placebo-controlled study of empagliflozin in renally impaired type 2 diabetes patients[a]

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Placebo**	**Empagliflozin 25 mg**
	eGFR ≥60 to <90 ml/min/1.73 m²			**eGFR ≥30 to <60 ml/min/1.73 m²**	
N	95	98	97	187	187
HbA1c (%)					
Baseline (mean)	8.09	8.02	7.96	8.04	8.03
Change from baseline[1]	0.06	-0.46	-0.63	0.05	-0.37
Difference from placebo[1] (95% CI)		-0.52* (-0.72, -0.32)	-0.68* (-0.88, -0.49)		-0.42* (-0.56, -0.28)
N	89	94	91	178	175
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	6.7	17.0	24.2	7.9	12.0
N	95	98	97	187	187
Body Weight (kg)[2]					
Baseline (mean)	86.00	92.05	88.06	82.49	83.22
Change from baseline[1]	-0.33	-1.76	-2.33	-0.08	-0.98
Difference from placebo[1] (95% CI)		-1.43 (-2.09, -0.77)	-2.00 (-2.66, -1.34)		-0.91 (-1.41, -0.41)
N	95	98	97	187	187
SBP (mmHg)[2]					
Baseline (mean)	134.69	137.37	133.68	136.38	136.64
Change from baseline[1]	0.65	-2.92	-4.47	0.40	-3.88
Difference from placebo[1] (95% CI)		-3.57 (-6.86, -0.29)	-5.12 (-8.41, -1.82)		-4.28 (-6.88, -1.68)

a. Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

1. Mean adjusted for baseline value

2. Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure

* p<0.0001

Cardiovascular outcome

The double-blind, placebo-controlled EMPA-REG OUTCOME study compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with type 2 diabetes and established cardiovascular disease. A total of 7 020 patients were treated (empagliflozin 10 mg: 2 345, empagliflozin 25 mg: 2 342, placebo: 2 333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA1c was 8.1%, and 71.5% were male. At baseline, 74% of patients were being treated with metformin, 48% with insulin, and 43% with a 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.

At week 12, an adjusted mean (SE) improvement in HbA1c when compared to baseline of

0.11% (0.02) in the placebo group, 0.65% (0.02) and 0.71% (0.02) in the empagliflozin 10 and 25 mg groups was observed. After the first 12 weeks glycaemic control was optimized independent of investigative treatment. Therefore the effect was attenuated at week 94, with an adjusted mean (SE) improvement in HbA1c of 0.08% (0.02) in the placebo group, 0.50% (0.02) and 0.55% (0.02) in the empagliflozin 10 and 25 mg groups.

Empagliflozin was superior in preventing the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg (Figure 1) and confirmed by an improved overall survival. The effect of empagliflozin on the primary combined endpoint of CV death, non-fatal MI, or non-fatal stroke was largely independent of glycaemic control or renal function (eGFR) and generally consistent across eGFR categories down to an eGFR of 30 ml/min/1.73 m^2 in the EMPA-REG OUTCOME study.

The efficacy for preventing cardiovascular mortality has not been conclusively established in patients using empagliflozin concomitantly with DPP-4 inhibitors or in Black patients because the representation of these groups in the EMPA-REG OUTCOME study was limited.

Table 12: Treatment effect for the primary composite endpoint, its components and mortality[a]

	Placebo	**Empagliflozin[b]**
N	2 333	4 687
Time to first event 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)

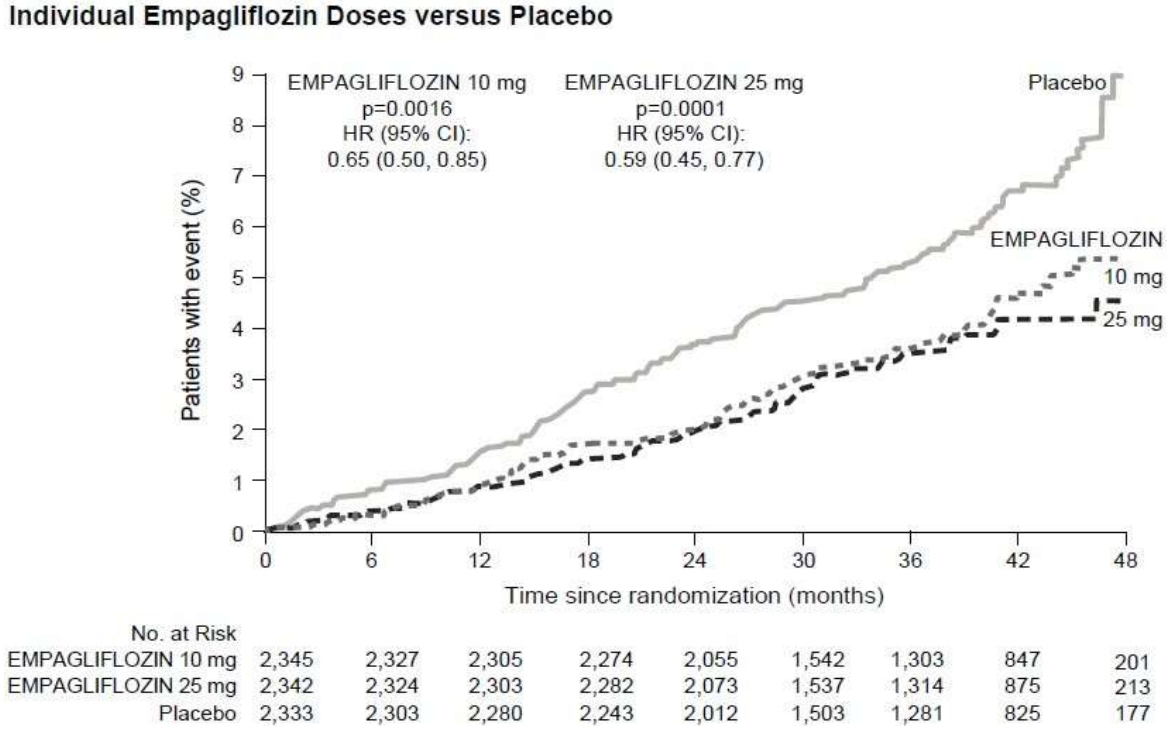
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
Non-CV mortality N (%)	57 (2.4)	97 (2.1)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.16)

CV = cardiovascular, MI = myocardial infarction

a. Treated set (TS), i.e. patients who had received at least one dose of study drug
b. Pooled doses of empagliflozin 10 mg and 25 mg

*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 cardiovascular death in the EMPA-REG OUTCOME study



Heart failure requiring hospitalisation

In the EMPA-REG OUTCOME study, empagliflozin reduced the risk of heart failure requiring hospitalisation compared with placebo (empagliflozin 2.7 %; placebo 4.1 %; HR 0.65, 95 % CI 0.50, 0.85).

Nephropathy

In the EMPA-REG OUTCOME study, for time to first nephropathy event, the HR was 0.61 (95 % CI 0.53, 0.70) for empagliflozin (12.7 %) vs placebo (18.8 %).

In addition, empagliflozin showed a higher (HR 1.82, 95 % CI 1.40, 2.37) occurrence of sustained normo- or micro-albuminuria (49.7 %) in patients with baseline macro-albuminuria compared with placebo (28.8 %).

Fasting plasma glucose

In four placebo-controlled studies, treatment with empagliflozin as monotherapy or add-on therapy to metformin, pioglitazone, or metformin plus a sulphonylurea resulted in mean

changes from baseline in FPG of -20.5 mg/dl [-1.14 mmol/l] for empagliflozin 10 mg and -23.2 mg/dl [-1.29 mmol/l] for empagliflozin 25 mg compared to placebo (7.4 mg/dl [0.41 mmol/l]). This effect was observed after 24 weeks and maintained for 76 weeks.

2-hour post-prandial glucose

Treatment with empagliflozin as add-on to metformin or metformin and a sulphonylurea resulted in a clinically meaningful reduction of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin: placebo +5.9 mg/dl, empagliflozin 10 mg: -46.0 mg/dl, empagliflozin 25 mg: -44.6 mg/dl, add-on to metformin and a sulphonylurea: placebo -2.3 mg/dl, empagliflozin 10 mg: -35.7 mg/dl, empagliflozin 25 mg: -36.6 mg/dl).

Patients with high baseline HbA1c >10%

In a pre-specified pooled analysis of three phase 3 studies, treatment with open-label empagliflozin 25 mg in patients with severe hyperglycaemia (N=184, mean baseline HbA1c

11.15%) resulted in a clinically meaningful reduction in HbA1c from baseline of 3.27% at week 24; no placebo or empagliflozin 10 mg arms were included in these studies.

Body weight

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

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 and up to 2 antihypertensive therapies. Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c, and 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring. Treatment with empagliflozin provided reductions in seated SBP and DBP.

Table 13: Efficacy results at 12 week in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure[a]

	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	271	276	276
HbA1c (%) at week 12[1]			
Baseline (mean)	7.90	7.87	7.92
Change from baseline[2]	0.03	-0.59	-0.62
Difference from placebo[2] (95% CI)		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour SBP at week 12[3]			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[4]	0.48	-2.95	-3.68

	Placebo	Empagliflozin	
		10 mg	25 mg
Difference from placebo[4] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour DBP at week 12[3]			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[5]	0.32	-1.04	-1.40
Difference from placebo[5] (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

a. Full analysis set (FAS)
1. LOCF, values after taking antidiabetic rescue therapy censored
2. Mean adjusted for baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products
3. LOCF, values after taking antidiabetic rescue therapy or changing antihypertensive rescue therapy censored
4. Mean adjusted for baseline SBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products
5. Mean adjusted for baseline DBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products

* p-value <0.0001

** p-value <0.001

In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin 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 52.

Heart failure

Empagliflozin in patients with heart failure and reduced ejection fraction

A randomised, double-blind, placebo-controlled study (EMPEROR-Reduced) was conducted in 3 730 patients with chronic heart failure (New York Heart Association [NYHA] II-IV) and reduced ejection fraction (LVEF ≤40%) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care heart failure therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent) and eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline were included in the confirmatory testing. Heart Failure therapy at baseline included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (88.3%), beta blockers (94.7%), mineralocorticoid receptor antagonists (71.3%) and diuretics (95.0%).

A total of 1 863 patients were randomised to empagliflozin 10 mg (placebo: 1 867) and followed for a median of 15.7 months. The study population consisted of 76.1% men and 23.9% women with a mean age of 66.8 years (range: 25-94 years), 26.8% were 75 years of age or older. 70.5% of the study population were White, 18.0% Asian and 6.9% Black/African American. At randomisation, 75.1% of patients were NYHA class II, 24.4% were class III and

0.5% were class IV. The mean LVEF was 27.5%. At baseline, the mean eGFR was 62.0 ml/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. About half of the patients (51.7%) had an eGFR of ≥60 ml/min/1.73 m^2, 24.1% of 45 to <60 ml/min/1.73 m^2, 18.6% of 30 to <45 ml/min/1.73 m^2 and 5.3% 20 to <30 ml/min/1.73 m^2.

Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline.

Table 14: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

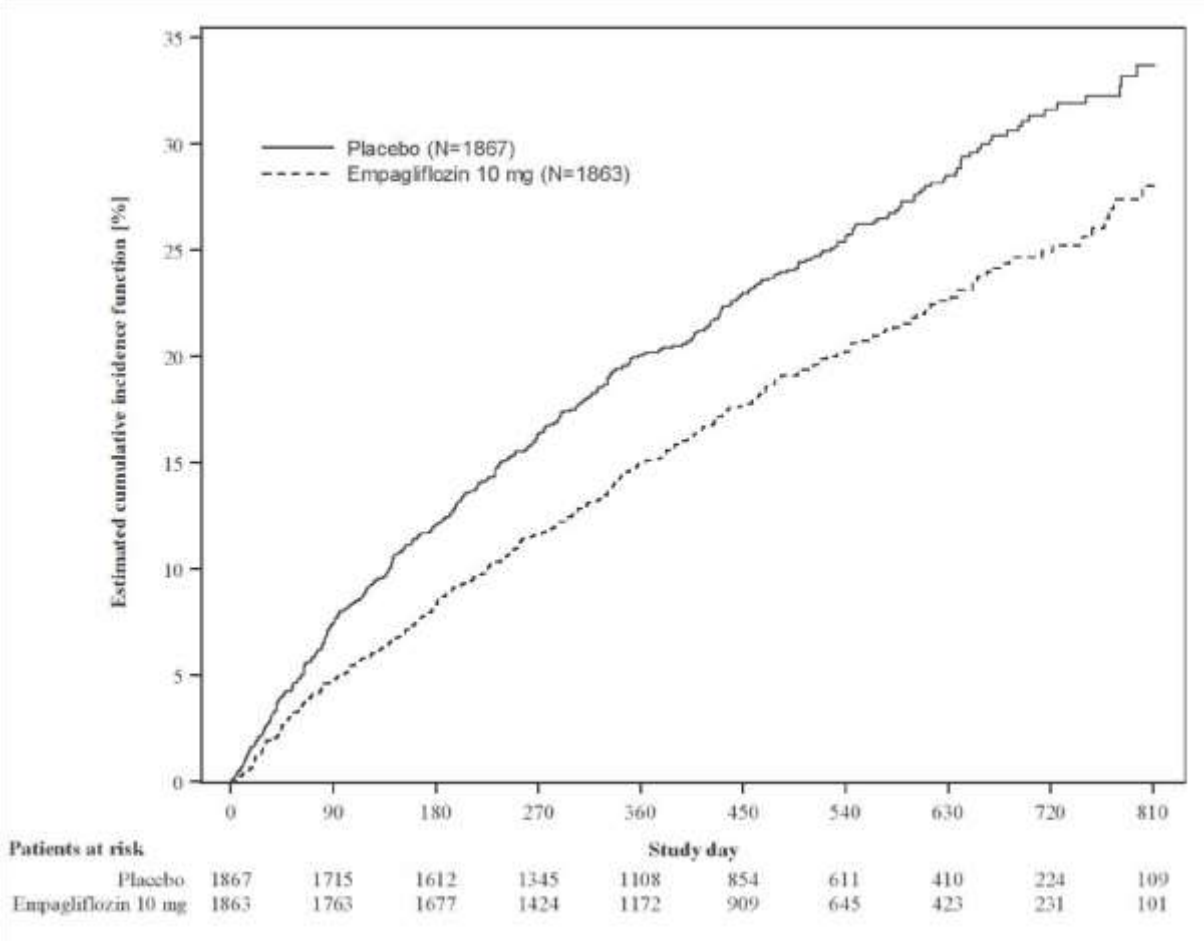
	Placebo	**Empagliflozin 10 mg**
N	1 867	1 863
Time to first event of CV death or HHF, N (%)	462 (24.7)	361 (19.4)
Hazard ratio vs. placebo (95% CI)*		0.75 (0.65, 0.86)
p−value for superiority		<0.0001
CV Death, N (%)	202 (10.8)	187 (10.0)
Hazard ratio vs. placebo (95% CI)		0.92 (0.75, 1.12)
HHF (first occurrence), N (%)	342 (18.3)	246 (13.2)
Hazard ratio vs. placebo (95% CI)		0.69 (0.59, 0.81)
HHF (first and recurrent), N of events	553	388
Hazard ratio vs. placebo (95% CI)*		0.70 (0.58, 0.85)
p−value		0.0003
eGFR (CKD-EPI)cr slope, Rate of decline (ml/min/1.73m^2/year)**	-2.28	-0.55
Treatment difference vs. placebo (95% CI)		1.73 (1.10, 2.37)
p-value		< 0.0001

CV = cardiovascular, HHF = hospitalisation for heart failure, eGFR = Estimated glomerular filtration rate, CKD EPI = Chronic kidney disease epidemiology collaboration equation

* CV death and HHF events were adjudicated by an independent clinical event committee and analysed based on the randomised set.

**eGFR slope was analysed based on the treated set. Intercept is -0.95 ml/min/1.73 m^2 for placebo and -3.02 ml/min/1.73 m^2 for empagliflozin. The intercept represents the acute effect on eGFR while the slope represents the long-term effect.

Figure 2 Time to first event of adjudicated CV death or HHF



The results of the primary composite endpoint were generally consistent with a hazard ratio (HR) below 1 across the pre-specified subgroups, including patients with heart failure, with or without type 2 diabetes mellitus and with or without renal impairment (down to an eGFR of 20 ml/min/1.73 m^2).

Empagliflozin in patients with heart failure and preserved ejection fraction

A randomised, double-blind, placebo-controlled study (EMPEROR-Preserved) was conducted in 5 988 patients with chronic heart failure (NYHA II-IV) and preserved ejection fraction (LVEF >40%) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent), and eGFR (CKD-EPI)cr slope of change from baseline were included in the confirmatory testing. Baseline therapy included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (80.7%), beta blockers (86.3%), mineralocorticoid receptor antagonists (37.5%) and diuretics (86.2%).

A total of 2 997 patients were randomised to empagliflozin 10 mg (placebo: 2 991) and followed for a median of 26.2 months. The study population consisted of 55.3% men and 44.7% women with a mean age of 71.9 years (range: 22-100 years), 43.0% were 75 years of age or older. 75.9% of the study population were White, 13.8% Asian and 4.3% Black/African American. At randomisation, 81.5% of patients were NYHA class II, 18.1% were class III and 0.3% were class IV. The EMPEROR-Preserved study population included patients with a LVEF <50% (33.1%), with a LVEF 50 to <60% (34.4%) and a LVEF ≥60% (32.5%). At baseline, the mean eGFR was 60.6 ml/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 21 mg/g. About half of the patients (50.1%) had an eGFR of ≥60

ml/min/1.73 m^2, 26.1% of 45 to <60 ml/min/1.73 m^2, 18.6% of 30 to <45 ml/min/1.73 m^2 and 4.9% 20 to <30 ml/min/1.73 m^2.

Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline.

Table 15: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

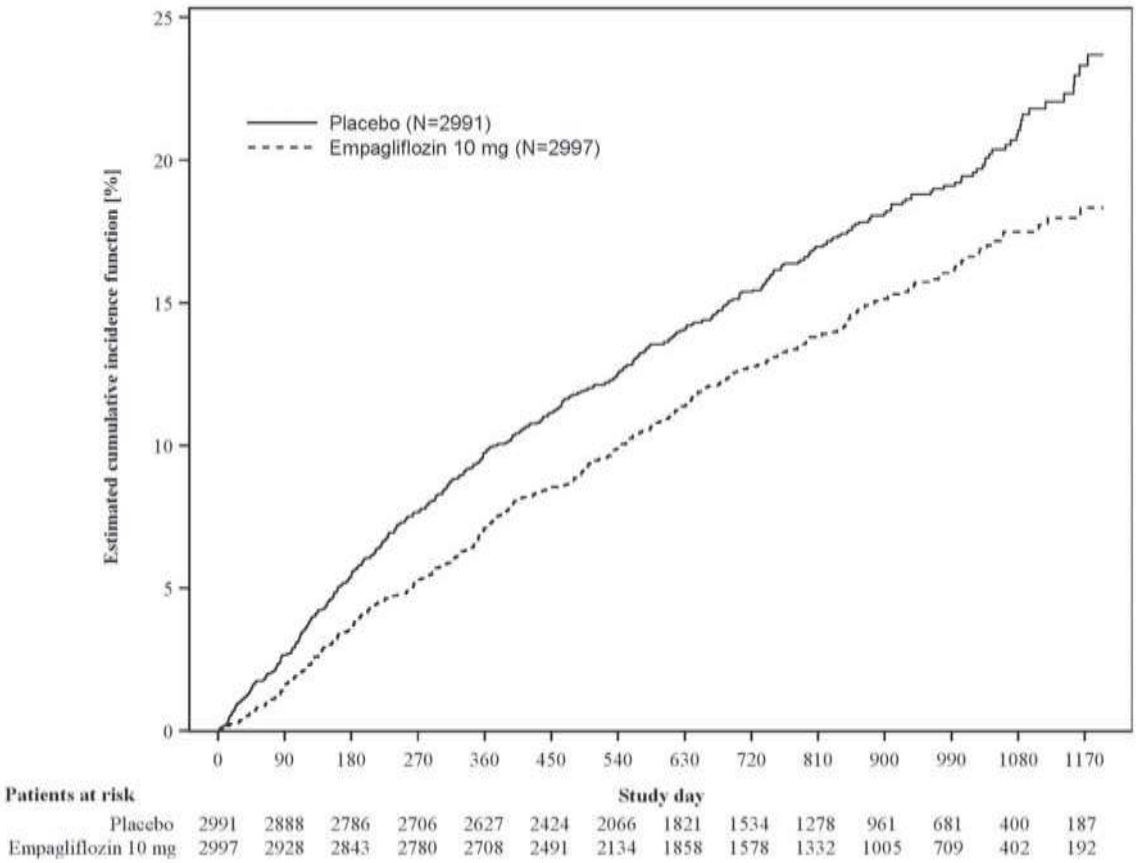
	Placebo	**Empagliflozin 10 mg**
N	2 991	2 997
Time to first event of CV death or HHF, N (%)	511 (17.1)	415 (13.8)
Hazard ratio vs. placebo (95% CI)*		0.79 (0.69, 0.90)
p−value for superiority		0.0003
CV Death, N (%)	244 (8.2)	219 (7.3)
Hazard ratio vs. placebo (95% CI)		0.91 (0.76, 1.09)
HHF (first occurrence), N (%)	352 (11.8)	259 (8.6)
Hazard ratio vs. placebo (95% CI)		0.71 (0.60, 0.83)
HHF (first and recurrent), N of events	541	407
Hazard ratio vs. placebo (95% CI)*		0.73 (0.61, 0.88)
p−value		0.0009
eGFR (CKD-EPI)cr slope, Rate of decline (ml/min/1.73m^2/year)**	-2.62	-1.25
Treatment difference vs. placebo (95% CI)		1.36 (1.06, 1.66)
p-value		< 0.0001

CV = cardiovascular, HHF = hospitalisation for heart failure, eGFR = Estimated glomerular filtration rate, CKD EPI = Chronic kidney disease epidemiology collaboration equation

* CV death and HHF events were adjudicated by an independent clinical event committee and analysed based on the randomised set.

**eGFR slope was analysed based on the treated set. Intercept is -0.18 ml/min/1.73 m^2 for placebo and -3.02 ml/min/1.73 m^2 for empagliflozin. The intercept represents the acute effect on eGFR while the slope represents the long-term effect.

Figure 3 Time to first event of adjudicated CV death or HHF



The results of the primary composite endpoint were consistent across each of the prespecified subgroups categorized by e.g., LVEF, diabetes status or renal function (down to an eGFR of 20 ml/min/1.73 m^2).

Chronic kidney disease

A randomised, double-blind, placebo-controlled study of empagliflozin 10 mg once daily

(EMPA-KIDNEY) was conducted in 6 609 patients with chronic kidney disease (eGFR ≥20 - <45 ml/min/1.73 m^2; or eGFR ≥45 - <90 ml/min/1.73 m^2 with urinary albumin to creatinine ratio (UACR) ≥200 mg/g) to assess cardio-renal outcomes as adjunct to standard of care therapy. The primary endpoint was the time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomisation, sustained eGFR <10 ml/min/1.73 m^2, end-stage kidney disease, or renal death) or CV death. First occurrence of hospitalisation for heart failure or CV death, all-cause hospitalisation (first and recurrent), and all-cause mortality were included in the confirmatory testing. Baseline therapy included an appropriate use of a RAS-inhibitor (85.2% ACE inhibitor or angiotensin receptor blocker).

A total of 3 304 patients were randomised to empagliflozin 10 mg (placebo: 3 305) and followed for a median of 24.3 months. The study population consisted of 66.8% men and 33.2% women with a mean age of 63.3 years (range: 18-94 years), 23.0% were 75 years of age or older. 58.4% of the study population were White, 36.2% Asian and 4.0% Black/African American.

At baseline, the mean eGFR was 37.3 ml/min/1.73 m^2, 21.2% patients had an eGFR of ≥45 ml/min/1.73 m^2, 44.3% of 30 to <45 ml/min/1.73 m^2 and 34.5% <30 ml/min/1.73 m^2 including 254 patients with an eGFR <20 ml/min /1.73 m^2. The median UACR was 329 mg/g,

20.1% patients had an UACR <30 mg/g, 28.2% had an UACR 30 to ≤300 mg/g and 51.7% had an UACR >300 mg/g; 41.1% of patients had an UACR <200 mg/g. Primary causes of CKD were diabetic nephropathy/diabetic kidney disease (31%), glomerular disease (25%), hypertensive/renovascular disease (22%) and other/unknown (22%).

Empagliflozin was superior in reducing the risk of the primary composite endpoint of kidney disease progression or CV death compared with placebo. Additionally, empagliflozin significantly reduced the risk of all-cause hospitalisation (first and recurrent).

Table 16: Treatment effect for the primary composite and key secondary endpoints included in the pre-specified confirmatory testing and its components

	Placebo	**Empagliflozin 10 mg**
	3 305	3 304
Time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomisation, sustained eGFR <10 ml/min/1.73 m^2, end-stage kidney disease* (ESKD), or renal death) or CV death, N (%)	558 (16.9)	432 (13.1)
Hazard ratio vs. placebo (99.83% CI)		0.72 (0.59, 0.89)
p−value for superiority		<0.0001
Sustained ≥40% eGFR decline from randomisation, N (%)	474 (14.3)	359 (10.9)
Hazard ratio vs. placebo (95% CI)		0.70 (0.61, 0.81)
p-value		<0.0001
ESKD* or sustained eGFR <10 ml/min/1.73 m^2, N (%)	221 (6.7)	157 (4.8)
Hazard ratio vs. placebo (95% CI)		0.69 (0.56, 0.84)
p-value		0.0003
Renal death, N (%)**	4 (0.1)	4 (0.1)
Hazard ratio vs. placebo (95% CI)		
p-value		
CV Death, N (%)	69 (2.1)	59 (1.8)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.19)
p-value		0.3366
ESKD or CV Death, N (%)[#]	217 (6.6)	163 (4.9)
Hazard ratio vs. placebo (95% CI)		0.73 (0.59, 0.89)
p-value		0.0023
Occurrence of all-cause hospitalisation (first and recurrent), N of events	1 895	1 611
Hazard ratio vs. placebo (99.03% CI)		0.86 (0.75, 0.98)

p-value		0.0025

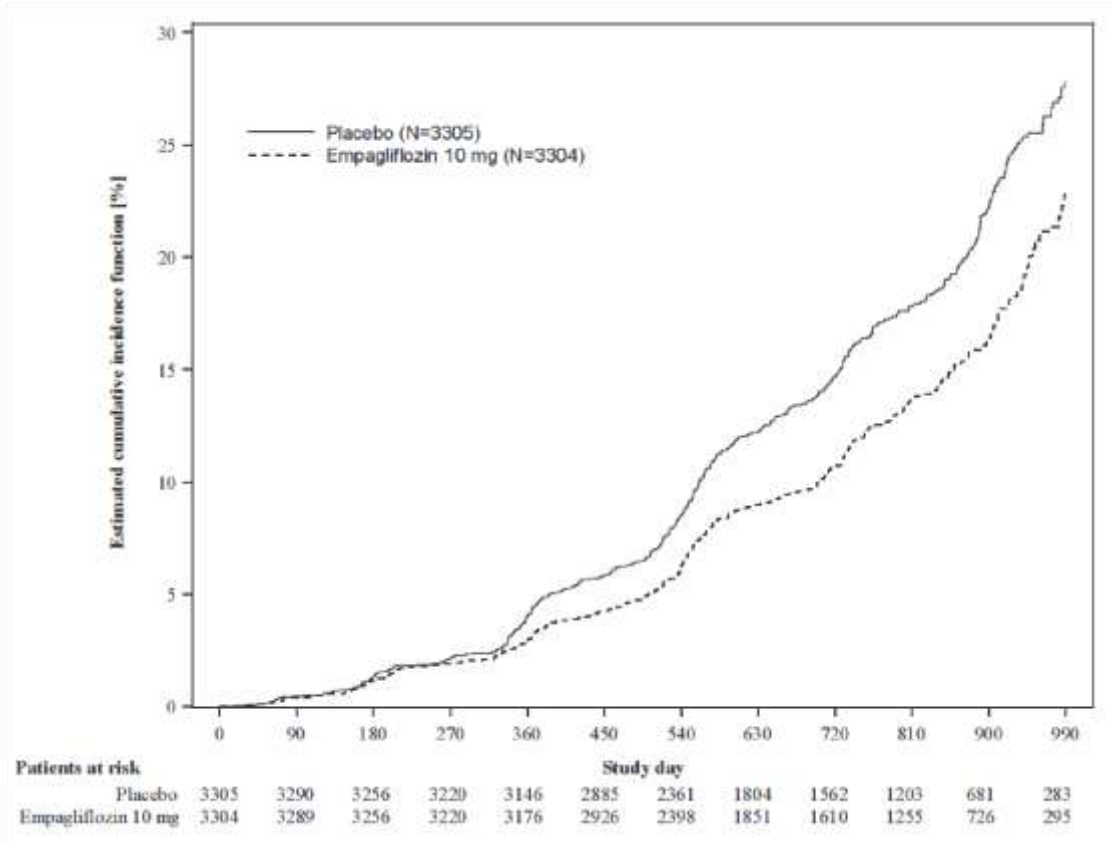
CV = cardiovascular, HHF = hospitalisation for heart failure, eGFR = Estimated glomerular filtration rate

* End-stage kidney disease (ESKD) is defined as the initiation of maintenance dialysis or receipt of a kidney transplant.

** There were too few events of renal death to compute a reliable hazard ratio.

Predefined as one of the two stopping criteria in the pre-planned interim analysis.

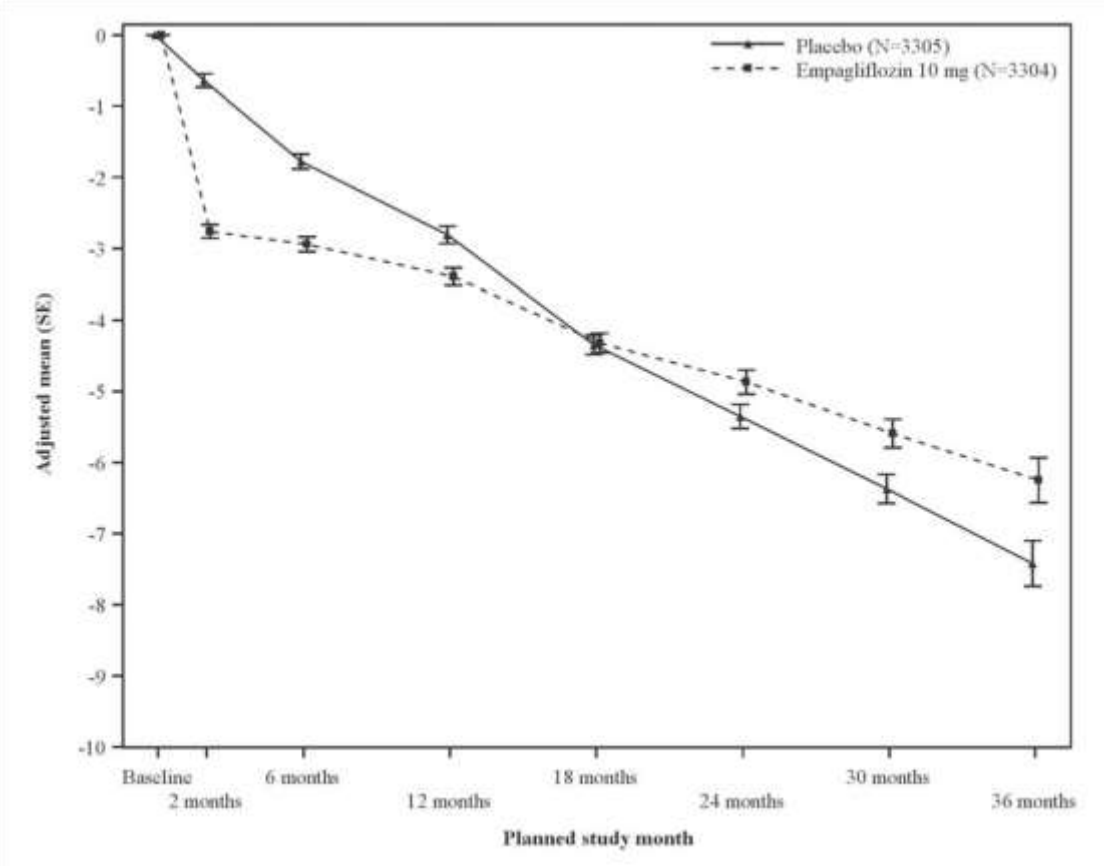
Figure 4 Time to first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function



The results of the primary composite endpoint were generally consistent across the prespecified subgroups, including eGFR categories, underlying cause of renal disease, diabetes status, or background use of RAS inhibitors. Treatment benefits were more clearly evident in patients with higher levels of albuminuria.

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (Figure 5). Empagliflozin slowed the annual rate of eGFR decline compared to placebo by 1.37 ml/min/1.73 m^2/year (95% CI 1.16, 1.59), based on a prespecified analysis of all eGFR measurements taken from the 2-month visit to the final followup visit. Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation as demonstrated in several of the empagliflozin studies, supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

Figure 5 Change in eGFR over time*



*eGFR (CKD-EPI) (ml/min/1.73 m) MMRM results over time - randomised set.

Sitagliptin

Clinical efficacy and safety

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment in adult patients with type 2 diabetes.

Two studies were conducted to evaluate the efficacy and safety of sitagliptin monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (2-hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

Sitagliptin 100 mg once daily provided significant improvements in glycaemic parameters compared with placebo in two 24-week studies of sitagliptin as add-on therapy, one in combination with metformin and one in combination with pioglitazone. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In these studies there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

A 24-week placebo-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride alone or glimepiride in combination with metformin. The addition of sitagliptin to either glimepiride alone or to glimepiride and

metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

A 26-week placebo-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycaemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycaemia was also similar in patients treated with sitagliptin or placebo.

A 24-week placebo-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

In a 24-week placebo-controlled reported factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

A 24-week active (metformin)-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin 100 mg once daily (N=528) compared to metformin (N=522) in patients with inadequate glycaemic control on diet and exercise and who were not on anti-hyperglycaemic therapy (off therapy for at least 4 months). The mean dose of metformin was approximately 1,900 mg per day. The reduction in HbA1c from mean baseline values of 7.2 % was -0.43 % for sitagliptin and -0.57 % for metformin (Per Protocol Analysis). The overall incidence of gastrointestinal adverse reactions considered as drug-related in patients treated with sitagliptin was 2.7 % compared with 12.6 % in patients treated with metformin. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 1.3 %; metformin, 1.9 %). Body weight decreased from baseline in both groups (sitagliptin, -0.6 kg; metformin -1.9 kg).

In a reported study comparing the efficacy and safety of the addition of sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA1c. The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of $\leq$ 5 mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 vs. +1.1 kg). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

A 24-week placebo-controlled reported study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin

therapy. Baseline HbA1c was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. At Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA1c in patients treated with sitagliptin and insulin (with or without metformin) was -1.31 % compared to -0.87 % in patients treated with placebo and insulin (with or without metformin), a difference of -0.45 % [95 % CI: -0.60, -0.29]. The incidence of hypoglycaemia was 25.2 % in patients treated with sitagliptin and insulin (with or without metformin) and 36.8 % in patients treated with placebo and insulin (with or without metformin). The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.1 %). There was no difference in the incidence of severe hypoglycaemia.

A reported study comparing sitagliptin at 25 or 50 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in patients with moderate to severe renal impairment. This study involved 423 patients with chronic renal impairment (estimated glomerular filtration rate < 50 mL/min). After 54 weeks, the mean reduction from baseline in HbA1c was -0.76 % with sitagliptin and -0.64 % with glipizide (Per-Protocol Analysis). In this study, the efficacy and safety profile of sitagliptin at 25 or 50 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia in the sitagliptin group (6.2 %) was significantly lower than that in the glipizide group (17.0 %). There was also a significant difference between groups with respect to change from baseline body weight (sitagliptin -0.6 kg; glipizide +1.2 kg).

Another reported study comparing sitagliptin at 25 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in 129 patients with ESRD who were on dialysis. After 54 weeks, the mean reduction from baseline in HbA1c was -0.72 % with sitagliptin and -0.87 % with glipizide. In this study, the efficacy and safety profile of sitagliptin at 25 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 6.3 %; glipizide, 10.8 %).

In another reported study involving 91 patients with type 2 diabetes and chronic renal impairment (creatinine clearance < 50 mL/min), the safety and tolerability of treatment with sitagliptin at 25 or 50 mg once daily were generally similar to placebo. In addition, after 12 weeks, the mean reductions in HbA1c (sitagliptin -0.59 %; placebo -0.18 %) and FPG (sitagliptin -25.5 mg/dL; placebo -3.0 mg/dL) were generally similar to those observed in other monotherapy studies in patients with normal renal function.

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an HbA1c of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m2) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m2).

Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual

components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes.

Paediatric population

A 54-week, double-blind reported study was conducted to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti hyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks.

Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3).

5.3. Pharmacokinetic properties

Empagliflozin

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 1.5 hours 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 1 870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4 740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic 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.

Administration of empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} 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 the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Biotransformation

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-, 3-, 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 UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour.

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 volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). 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.

Special populations

Renal impairment

In patients with mild, moderate or severe renal impairment (eGFR <30 - <90 ml/min/1.73 m^2) and patients with kidney failure/end stage kidney disease (ESKD), 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/ESKD 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. 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.

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.

Body Mass Index

Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. In this analysis, AUC was estimated to be 5.82%, 10.4%, and 17.3% lower in subjects with BMI of 30, 35, and 45 kg/m^2, respectively, compared to subjects with a body mass index of 25 kg/m^2.

Gender

Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race

In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25 kg/m^2 compared to non-Asians with a body mass index of 25 kg/m^2.

Elderly

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

Paediatric population

A paediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 Mm.hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C]sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

In reported *In vitro* data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (GFR ≥ 60 to < 90 mL/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), and approximately 4-fold in patients with severe renal impairment (GFR < 30 mL/min), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose).

Hepatic impairment

No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly

No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric population

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients < 10 years of age.

Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.

Other patient characteristics with sitagliptin

No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a reported composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Empagliflozin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.

In long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including 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 and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic.

In a 2 year carcinogenicity study, empagliflozin did not increase the incidence of tumours in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72-times the maximal clinical AUC exposure to empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumours in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both 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 1 000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1 000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. 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.

At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.

In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No

such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.

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.

Sitagliptin

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No treatment related effects on fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

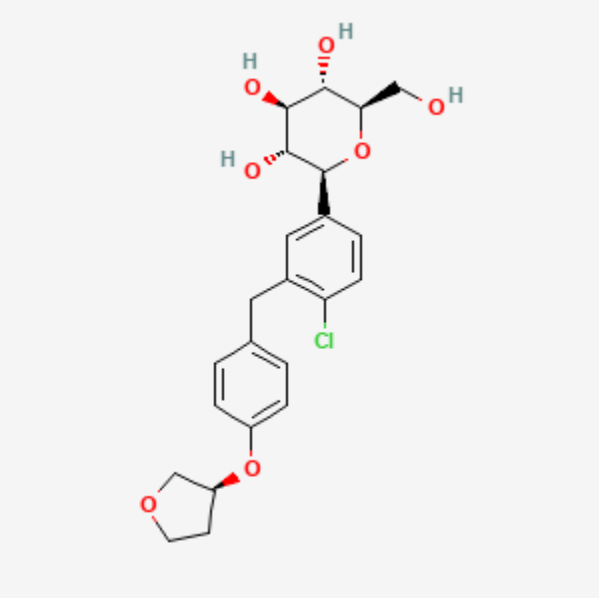
In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

7. Description

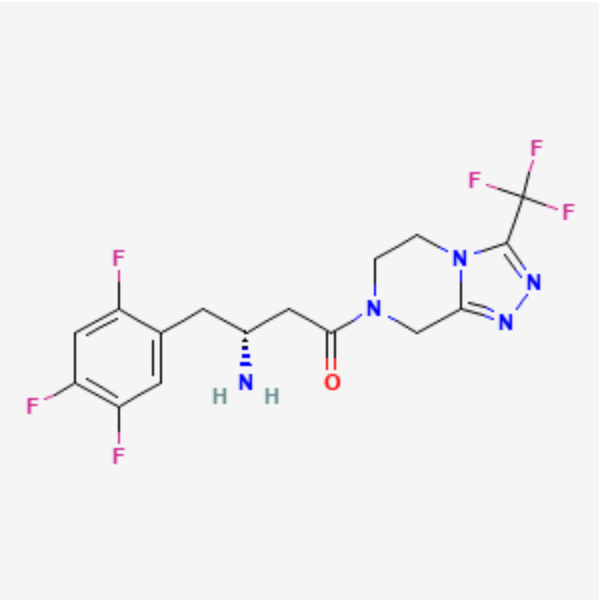
Empagliflozin:

Empagliflozin is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-[(3S)-oxolan-3 yl] oxyphenyl] methyl]phenyl] -6-(hydroxymethyl)oxane-3,4,5-triol.The empirical formula is $C_{23}H_{27}ClO_7$ and its molecular weight is 450.9 g/mol. The chemical structure of empagliflozin is:



Sitagliptin

Sitagliptin (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin -7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one. The empirical formula is $C_{16}H_{15}F_6N_5O$ and its molecular weight is 407.31 g/mol. The chemical structure of Sitagliptin is:



Empazio S 25+100

Is peach colored, round, biconvex, film coated tablets,4 marking on one side and plain on other side . The excipients used are Colloidal silicon dioxide, Microcrystalline cellulose PH 101, Mannitol, croscarmellose sodium, Povidone K 30, Purified water, Magnesium stearate, Polyvinyl alcohol, Polyethylene glycol 6000,talc,titanium dioxide , red iron oxide

Empazio S 10+100

Is pink colored, round, biconvex, film coated tablets, 2 marking on one side and plain on other side The excipients used are Colloidal silicon dioxide, Microcrystalline cellulose PH 101, Mannitol 160C , croscarmellose sodium, Povidone K 30, Purified water, Magnesium stearate, Polyvinyl alcohol, Polyethylene glycol 6000,talc, titanium dioxide , Red iron oxide

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

Alu-PVC/PVDC Blister.

8.4. Storage and handing instructions

Store below 30°C.

Keep out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Pure and Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot no. 26A, 27-30, Sector-8A, IIE, SIDCUL,

Ranipur, Haridwar-249403 (Uttarakhand)

11. Details of permission or licence number with date

G/25/2011 issued on 23.09.2024

12. Date of revision

NA

MARKETED BY

Torrent Pharmaceuticals Limited.

IN/EMPAZIO S (25+100 /10+100)/Feb-2025 /01/PI