

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

SITAXA E/EMPAZIO S/COSPIAQ S

1. Generic Name

Empagliflozin and Sitagliptin Tablets 25 mg+100 mg

2. Qualitative and quantitative Composition:

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 List of excipients used are Colloidal Silicon Dioxide, Microcrystalline Cellulose, Mannitol, Croscarmellose Sodium, Povidone K, Magnesium Stearate, Polyvinyl Alcohol, Polyethylene Glycol , Talc, Titanium Dioxide, Red Iron Oxide and Yellow Iron Oxide.

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: 25 mg+100 mg

4. Clinical particulars

4.1. Therapeutic indication

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

4.2. Posology and method of administration

Posology

The recommended dose is one tablet daily. Each film coated tablet contains a fixed dose of Empagliflozin and Sitagliptin, the medication started as per the Physician's recommendation.

Method of Administration

It should be given orally once daily.

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 \geq 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, torsemide 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 *in 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 *in 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 *in 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.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), or very rare ($< 1/10\ 000$), and not known (cannot be estimated from the available data).

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

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 m²). 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

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

Table: 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

Adverse reaction	Frequency of adverse reaction
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 to 17 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 HbA_{1c} 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

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 (IC₅₀ 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 (PPAR γ) 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

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 m², 17.8% of 45-60 ml/min/1.73 m² and 7.7% of 30-45 ml/min/1.73 m².

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 hours mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring. Treatment with empagliflozin provided reductions in seated SBP and DBP.

Sitagliptin

General

In patients with type 2 diabetes, administration of Sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. In a 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. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes.

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of Sitagliptin 100 mg, Sitagliptin 800 mg (8 times the recommended dose), and placebo.

At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline was observed at 3 hours postdose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose. In patients with type 2 diabetes administered Sitagliptin 100 mg (N=81) or Sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

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 m²) 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/m², respectively, compared to subjects with a body mass index of 25 kg/m².

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/m² compared to non-Asians with a body mass index of 25 kg/m².

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 $t_{1/2}$ 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 ($IC_{50}=160 \mu M$) 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 \geq 60 to $<$ 90 mL/min) and patients with moderate renal impairment (GFR \geq 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 \geq 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 \leq 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.

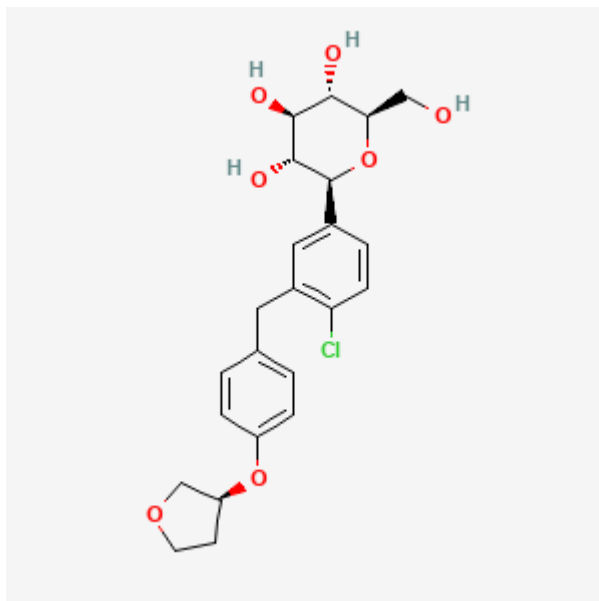
In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

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

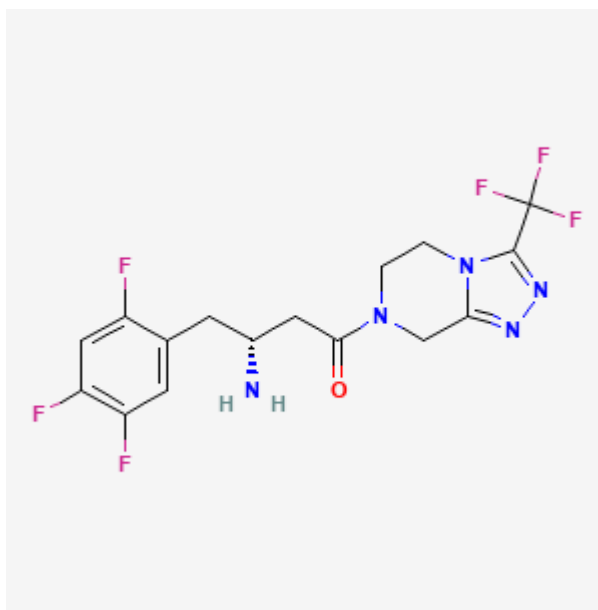
Empagliflozin:

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:



Empagliflozin and Sitagliptin Tablets are Peach colored, round, biconvex, film coated tablets, 4 making on one side and plain on other side.

The list of excipients used are Colloidal Silicon Dioxide, Microcrystalline Cellulose, Mannitol, Croscarmellose Sodium, Povidone K, Magnesium Stearate, Polyvinyl Alcohol, Polyethylene Glycol, Talc, Titanium Dioxide, Red Iron Oxide and Yellow 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

SITAXA E /EMPAZIO S/ COSPIAQ S is available in a pack of 10 tablets.

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

Exemed Pharmaceuticals,
Plot No. 133/1&133/2, G.I.D.C.,
Selvas Road, Vapi -396195,
Dist.: Valsad, State: Gujarat, India

11. Details of permission or licence number with date

Mfg. Lic. No. is G/25/2011, issued on 23.09.2024

12. Date of revision

NA

MARKETED BY

Torrent Pharmaceuticals Limited.

IN/SITAXA E/EMPAZIO S/COSPIAQ S (25 mg +100 mg)/MAY 2026/01/PI