Empaone 10 & 25 एम्पावन १०&२५ For Sale In India Only
Empagliflozin Tablets 10 mg & 25 mg

To be sold by retail on the prescription of a Registered Medical Practitioner only.

PRESCRIBING INFORMATION

1. GENERIC NAME

Empagliflozin Tablets 10 mg
Empagliflozin Tablets 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Empagliflozin Tablets 10 mg
Each film coated tablet contains
Empagliflozin ..... 10 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow USP-NF

Empagliflozin Tablets 25 mg
Each film coated tablet contains
Empagliflozin ..... 25 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow USP-NF

3. DOSAGE FORM AND STRENGTH

Empagliflozin is available as film coated tablets 10 mg and 25 mg.

4. CLINICAL PARTICULARS

4.1. Indications

Empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

4.2. Posology and Method of Administration

Posology

The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg.

When empagliflozin 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.

Method of administration

The tablets can be taken with or without food, swallowed whole with water. If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same day.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in the formulation.

4.4. Special Warnings and Precautions for Use

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients 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 DKA is more likely to occur with higher doses of empagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA 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 DKA 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 DKA while on SGLT-2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

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

Renal impairment

Empagliflozin should not be initiated in patients with an eGFR below 60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR is persistently below 60 ml/min/1.73 m^2 or CrCl <60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl persistently below 45 ml/min. Empagliflozin should not be used in patients with ESRD or in patients on dialysis as it is not expected to be effective in these patients.

Monitoring of renal function

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. Therefore assessment of renal function is recommended as follows:

- Prior to empagliflozin 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.

Risk for volume depletion

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

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin 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). Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended.

Urinary tract infections

In a pool of placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo and higher in patients treated with empagliflozin 10 mg. Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients 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 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.

Cardiac failure

Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. In the EMPA-REG OUTCOME study, 10.1% of the patients were reported with cardiac failure at baseline. The reduction of cardiovascular death in these patients was consistent with the overall study population.

Urine laboratory assessments

Due to its mechanism of action, patients taking empagliflozin 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.

Lactose

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product

4.5. Drug 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.

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

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.

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

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.

Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin.

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

Based on *in vitro* studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with active substances that are P-gp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in C_{max} of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 *in vitro* at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

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.

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 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 during pregnancy.

Breast-feeding

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

Fertility

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

Renal impairment

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. No dose adjustment is required for patients with an eGFR ≥60 ml/min/1.73 m^2 or CrCl ≥60 ml/min.

Empagliflozin should not be initiated in patients with an eGFR <60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 or CrCl below 60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl persistently below 45 ml/min.

Empagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in these patients.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this 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. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

Paediatric population

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

4.7. Effects on Ability to Drive and Use Machines

Empagliflozin 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 is used in combination with a sulphonylurea and/or insulin.

4.8. Undesirable Effects

Summary of the safety profile

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).

Tabulated list of adverse reactions

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 (Table 1).

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

System organ class	Very common	Common	Uncommon	Rare	Not known
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		Diabetic ketoacidosis*	
Skin and subcutaneous tissue disorders		Pruritus (generalised) Rash	Urticaria		Angioedema
Vascular disorders			Volume depletion[a]		
Renal and urinary disorders		Increased urination[a]	Dysuria		
Investigations		Serum lipids increased[b]	Blood creatinine increased/ Glomerular filtration rate decreased[a] Haematocrit increased[c]		

[a] see subsections below for additional information

[b] 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%.

[c] 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.

* 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 sulfonylurea (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).

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 sulfonylurea, 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 sulfonylurea (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).

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.

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%).

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.

Reporting of suspected 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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

Symptoms

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4 times the highest recommended daily dose) 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.

Therapy

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins, ATC code: A10BK03

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 5000 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. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

5.2 Pharmacodynamic Properties

Clinical efficacy and safety

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 prespecified 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.

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.

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 1000 mg; 12.5 mg and 500 mg, and 12.5 mg and 1000 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).

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.

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, $p<0.0001$).

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.

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.

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.

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 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) 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 sulfonylurea. 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 and confirmed by an improved overall survival (Table 10).

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.

Heart failure requiring hospitalization

In the EMPA-REG OUTCOME study, empagliflozin reduced the risk of heart failure requiring hospitalization 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 sulfonylurea 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.

5.3 PHARMACOKINETIC PROPERTIES

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 1870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. 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 renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. 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.

6. NONCLINICAL PROPERTIES

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 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1000 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.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

None

7.2 Packing Information

2's & 10's Blister Pack

7.3 STORAGE:

Do not store above 30°C.

8. PATIENT COUNSELING INFORMATION

Instructions

Instruct patients to read the Prescribing Information before starting empagliflozin therapy and to reread it each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Inform patients of the potential risks and benefits of empagliflozin and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take empagliflozin only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

Inform patients that the most common adverse reactions associated with the use of empagliflozin are urinary tract infections and mycotic genital infections.

Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with empagliflozin. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Advise women that breastfeeding is not recommended during treatment with empagliflozin.

Hypotension

Inform patients that hypotension may occur with empagliflozin and advise them to contact their healthcare provider if they experience such symptoms. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of empagliflozin, sometimes associated with illness or surgery among other risk factors.

Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue empagliflozin and seek medical attention immediately.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of empagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue empagliflozin use in those settings.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with empagliflozin. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria and angioedema, have been reported with empagliflozin. Advise patients to report immediately any skin reaction or angioedema, and to discontinue drug until they have consulted prescribing physician.

Laboratory Tests

Inform patients that renal function should be assessed prior to initiation of empagliflozin and monitored periodically thereafter.

Inform patients that elevated glucose in urinalysis is expected when taking empagliflozin.

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels toward the normal range. Hemoglobin A1c monitoring is especially useful for evaluating long-term glycemic control.

9. DETAILS OF MANUFACTURER

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10. DETAILS OF MANUFACTURING LICENCE NUMBER

TS/RR/2024-116346

11. DATE OF REVISION

June-2025