Approved Professional Information for Medicines for Human Use: AIZEMPA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINAL PRODUCT

AIZEMPA 10 mg film-coated tablets

AIZEMPA 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AIZEMPA 10 mg film-coated tablets

Each tablet contains 10 mg empagliflozin.

Contains sugar: lactose monohydrate 42,96 mg.

AIZEMPA 25 mg film-coated tablets

Each tablet contains 25 mg empagliflozin.

Contains sugar: lactose monohydrate 107,40 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

AIZEMPA 10 mg film-coated tablets

Pale Yellow, round, biconvex film-coated tablets debossed with "10" on one side and "A" on other side

AIZEMPA 25 mg film-coated tablets

Pale Yellow, oval, biconvex film-coated tablets debossed with "25" on one side and "A" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus

Glycaemic control:

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

Add-on combination therapy:

In combination with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulphonylurea, a DPP4 inhibitor, or insulin, when these together with diet and exercise do not provide adequate glycaemic control.

Prevention of cardiovascular events:

AIZEMPA is indicated in patients with type 2 diabetes mellitus and high cardiovascular risk* to reduce the risk of:

- cardiovascular death due to myocardial infarction
- cardiovascular death or hospitalisation for heart failure.

*e.g. previous myocardial infarction, multi vessel coronary artery disease, previous coronary revitalisation, single vessel coronary disease, at least 50 % narrowing of coronary artery lumen.

Heart failure (HF)

AIZEMPA is indicated in adult patients with heart failure (NYHA class II-IV) independent of left ventricular ejection fraction, with or without type 2 diabetes mellitus:

- to reduce the risk of cardiovascular death and hospitalisation for heart failure
- to slow kidney function decline.

4.2 Posology and method of administration

Posology

Assess hydration status and renal function before initiating treatment with AIZEMPA.

Do not initiate treatment in patients who are volume-depleted or acidotic (see below and section 4.4).

Type 2 diabetes mellitus indications:

The recommended starting dose of AIZEMPA is 10 mg once daily.

In patients tolerating AIZEMPA 10 mg once daily and requiring additional glycaemic control, the dose may be increased to 25 mg once daily.

Heart failure (HF) indication:

The recommended dose of AIZEMPA is 10 mg once daily.

Special populations

Patients with renal insufficiency:

For type 2 diabetes mellitus (T2DM) indications:

No dose adjustment is required for patients with eGFR ≥ 30 mL/min/1,73 m^2).

AIZEMPA is not recommended for use in patients with eGFR < 30 mL/min/1,73 m^2 (see section 4.3 and section 4.4).

HF indication:

AIZEMPA is not recommended for use in patients with eGFR < 20 mL/min/1,73 m^2 (see section 4.4).

There are insufficient data to support use in these patients.

Patients with hepatic insufficiency:

Dose adjustment may be necessary for patients with severe hepatic impairment.

Elderly Patients:

No dosage adjustment is recommended based on age. Therapeutic experience in patients aged 85 years and older is limited. Initiation of AIZEMPA therapy in this population is not recommended (see section 4.4).

Combination therapy:

When AIZEMPA is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see below and section 4.8).

Paediatric population:

Safety and effectiveness of AIZEMPA in children under 18 years of age have not been established.

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 empagliflozin or to any of the excipients listed in section 6.1.
- Treatment of type 1 diabetes mellitus.
- Treatment of ketoacidosis.
- Type 2 diabetes mellitus indications: Moderate and severe renal impairment (creatinine clearance < 30mL/min), end renal disease or dialysis.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

General

Empagliflozin should not be used in patients with type 1 diabetes mellitus (see "Diabetic Ketoacidosis" in section 4.4).

Diabetic ketoacidosis

Cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in

patients treated with AIZEMPA. In a number of cases, the presentation of the condition was atypical with increased blood glucose values, below 11 mmol/L (196 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 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 AIZEMPA 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. In both cases, treatment with AIZEMPA may be restarted once the patient's condition has stabilised.

Before initiating AIZEMPA, 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 SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of empagliflozin in patients with type 1 diabetes have not been established and empagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Renal impairment

Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR < 20 mL/min/1,73m^2.

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function.

Monitoring of renal function

Assessment of renal function is recommended as follows:

- Prior to empagliflozin initiation and periodically during treatment, i.e. at least 6-monthly
- Prior to initiation of any concomitant medicine that may have a negative impact on renal function.

Chronic kidney disease

Patients with albuminuria may benefit more from treatment with empagliflozin.

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 (see section 4.8).

Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure (see section 5.1). 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. Therefore, special attention should be given to their volume intake in case of co-administered medicine 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 (see section 4.2).

Urinary tract infections and genital infections:

The overall frequency of urinary tract infection, and/or genital infection, reported as an adverse event was higher than placebo in patients treated with AIZEMPA (see section 4.8), especially mycotic infections in females. Genital infections occurred more frequently in females than in males. Patients with a history of chronic or recurrent urinary tract infection (UTI) were more likely to experience UTI. Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin (see section 4.8). Temporary interruption of AIZEMPA 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, AIZEMPA 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 important to counsel all diabetic 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.

Infiltrative disease or Takotsubo cardiomyopathy

Patients with infiltrative disease or with Takotsubo cardiomyopathy have not been specifically studied. Therefore, efficacy in these patients has not been established.

Urine laboratory assessments

Due to its mechanism of action, patients taking AIZEMPA 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.

Paediatric population

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

Excipient lactose

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

Excipient sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Diuretics

Empagliflozin may add to the diuretic effect of hydrochlorothiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

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 (see sections 4.2 and 4.8).

Pharmacokinetic interactions

Effects of other medicines 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 of 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 on empagliflozin has not been studied. Co-treatment with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy.

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 medicines

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 health professional in order to monitor serum concentration of lithium.

Based on *in vitro* studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Medicine 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, medicine interactions with substrates of these uptake transporters are considered unlikely.

Interaction studies 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 Fertility, pregnancy and lactation

Pregnancy

AIZEMPA is contraindicated in 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 (see section 5.3).

Breastfeeding

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. AIZEMPA is contraindicated during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for AIZEMPA. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

AIZEMPA 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

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

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently reported adverse reaction was hypoglycaemia when used with sulphonylurea or insulin (see description of selected adverse reactions).

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with empagliflozin.

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Infections and infestations	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[4], urinary tract infection (including pyelonephritis and urosepsis)		Necrotising fasciitis of the perineum (Fournier's gangrene)*
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[2&3], thirst, weight loss	Diabetic ketoacidosis*	
Gastrointestinal disorders	Constipation		

Skin and subcutaneous tissue disorders	Pruritus (generalised), rash	Urticaria	Angioedema
Vascular disorders	Volume depletion[1]		
Renal and urinary disorders	Glycosuria, increased urination[5]	Dysuria, ketonuria, tubulo-interstitial nephritis	
Investigations	Serum lipids increased	Increased blood creatinine, decreased glomerular filtration rate[6], increased haematocrit[7]	

* see section 4.4

c) Description of selected adverse reactions

[1]*Volume depletion*

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was similar in patients treated with empagliflozin and placebo. The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients aged 75 years and older or those otherwise at risk. The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg or empagliflozin 25 mg compared to placebo.

[2]*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, add-on to basal insulin with or without metformin and with or without a sulphonylurea, and add-on to MDI insulin with or without metformin compared to placebo.
In the EMPEROR heart failure studies, similar frequency of hypoglycaemia was noted when used add-on to sulphonylurea or insulin compared to placebo.

[3]*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; and add-on to MDI insulin with or without metformin.

[4]*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 compared to

placebo. 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 than in patients without diabetes mellitus when treated with empagliflozin compared to placebo.

[5]*Increased urination*

Increased urination (including the predefined terms pollakiuria, polyuria, and nocturia) was observed at higher frequencies in patients treated with empagliflozin compared to placebo.
Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was similar for placebo and empagliflozin.
In the EMPEROR heart failure studies, increased urination was observed at similar frequencies in patients treated with empagliflozin and placebo.

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 and higher in empagliflozin 10 mg. 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.

[6]*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. 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 medicine discontinuation of treatment.

Consistently, in the EMPA-REG OUTCOME study, patients treated with empagliflozin experienced an initial fall in eGFR (mean: 3 mL/min/1,73 m^2). Thereafter, eGFR was maintained during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting acute haemodynamic changes may play a role in these renal function changes.

This phenomenon is also observed in the EMPEROR heart failure studies and the EMPA-KIDNEY study.

[7]*Haematocrit increased*

In the EMPA-REG Outcome study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

d) Paediatric population

In the DINAMO trial 157 children aged 10 years and above with type 2 diabetes were treated, in which 52 patients received empagliflozin, 52 linagliptin and 53 placebo. During the placebo-controlled phase, the most frequent adverse drug reaction was hypoglycaemia with higher overall rates for patients in the empagliflozin pooled group compared with placebo. None of these events was severe or required assistance.

Overall, the safety profile in children was similar to the safety profile in adults with type 2 diabetes mellitus.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za.

4.9 Overdose

Symptoms

The risk and severity of side effects may be increased (see section 4.8.)

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.

Treatment

In the event of an overdose, symptomatic and supportive treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied. Hypoglycaemia should be monitored for, especially when other antidiabetic medicine has been co-administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 21.2 Oral hypoglycaemics

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

ATC code: A10BK03

Mechanism of action

Empagliflozin is a reversible inhibitor of SGLT2 (sodium glucose cotransporter 2) with an IC50 of 1,3 nM. It has a 5 000-fold selectivity over human SGLT2 (IC50 of 6 278 nM), responsible for glucose absorption in the gut. Furthermore, high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues.

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 reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR (glomerular filtration rate). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine. The effect of empagliflozin in lowering blood glucose is independent of beta-cell function and insulin pathway.

Urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glycosuria observed with empagliflozin is accompanied by mild 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 sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values and beneficial effects on cardiac remodelling, filling pressures and diastolic function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial effects observed independent of left ventricular ejection fraction (LVEF).

5.2 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. For single doses of 10 mg and 25 mg, the terminal phase half-life is 13,1 ± 4,0 h and 10,2 ± 2,1 h respectively. 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 36,8 % and plasma protein binding was 86,2 %.

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 95,6 % of the drug-related radioactivity was eliminated in faeces (41,2 %) or urine (54,4 %). The majority of drug-related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Special populations

Renal impairment

In patients with mild (eGFR: 60 - < 90 mL/min/1,73 m^2), moderate (eGFR: 30 - < 60 mL/min/1,73 m^2), severe (eGFR: < 30 mL/ min/1,73 m^2) renal impairment and patients with kidney failure/ ESRD (end stage renal disease) patients, AUC of empagliflozin increased by approximately 18 %, 20 %, 66 %, and 48 %, respectively, compared to subjects with normal renal function.

Hepatic impairment

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23 %, 47 %, and 75 % and C_{max} by approximately 4 %, 23 %, and 48 %, respectively, compared to subjects with normal hepatic function. Based on pharmacokinetics, dosage adjustments may be necessary in patients with severe hepatic impairment.

Body Mass Index

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

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

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

5.3 Preclinical safety data

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 embryofoetal 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 medicine-free recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Microcrystalline cellulose

Povidone

Croscarmellose sodium

Colloidal silicon dioxide

Magnesium stearate

Film coating

Hypromellose

Titanium dioxide

Talc

Macrogol

Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister packs in the outer carton until required for use.

Keep the bottle tightly closed to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC-peel push blister pack or HDPE Container with 33 mm CR closure

Pack sizes of 10, 28, 30, 56, 60, 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBERS

AIZEMPA 10 mg: 54/21.2/0651

AIZEMPA 25 mg: 54/21.2/0652

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 August 2020

10. DATE OF REVISION OF THE TEXT

19 February 2025