SUMMARY OF THE PRODUCT CHARACTERISTICS (SPCs)

XENGLU TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Xenglu 10mg Tablet
Xenglu 25mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Empagliflozin

Xenglu 10mg Tablet:
Each film coated tablet contains:
Empagliflozin ……. 10mg

Xenglu 25mg Tablet:
Each film coated tablet contains:
Empagliflozin ……. 25mg

3. PHARMACEUTICAL FORM

Tablets

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.
Limitation of Use EMPAGLIFLOZIN is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

4.2 Dosage and administration

Recommended Dosage
The recommended dose of EMPAGLIFLOZIN is 10 mg once daily in the morning, taken with or without food. In patients tolerating EMPAGLIFLOZIN, the dose may be increased to 25 mg. In patients with volume depletion, correcting this condition prior to initiation of EMPAGLIFLOZIN is recommended.
Patients with Renal Impairment Assessment of renal function is recommended prior to initiation of EMPAGLIFLOZIN and periodically thereafter. EMPAGLIFLOZIN should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m2. No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m2. EMPAGLIFLOZIN should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m2.

4.3 Contraindications

- History of serious hypersensitivity reaction to EMPAGLIFLOZIN.
- Severe renal impairment, end-stage renal disease, or dialysis.

4.4 Special warnings and precautions for use

Hypotension EMPAGLIFLOZIN causes intravascular volume contraction. Symptomatic hypotension may occur after initiating EMPAGLIFLOZIN particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating EMPAGLIFLOZIN, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Impairment in Renal Function EMPAGLIFLOZIN increases serum creatinine and decreases eGFR. The risk of impaired renal function with EMPAGLIFLOZIN is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients. Renal function should be evaluated prior to initiating EMPAGLIFLOZIN and periodically thereafter.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when EMPAGLIFLOZIN is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with EMPAGLIFLOZIN.

Genital Mycotic Infections EMPAGLIFLOZIN increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.

Urinary Tract Infections EMPAGLIFLOZIN increases the risk for urinary tract infections. Monitor and treat as appropriate.

Increased Low-Density Lipoprotein Cholesterol (LDL-C) Increases in LDL-C can occur with EMPAGLIFLOZIN. Monitor and treat as appropriate.

Macrovascular Outcomes There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with EMPAGLIFLOZIN or any other antidiabetic drug.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Insulin or Insulin Secretagogues Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.

Positive Urine Glucose Test Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

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

4.6 Use in Special Populations:

Pregnancy

Pregnancy Category C There are no adequate and well-controlled studies of EMPAGLIFLOZIN in pregnant women. EMPAGLIFLOZIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

Empagliflozin was not teratogenic in embryo-fetal development studies in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg. At higher doses, causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154 times the 25 mg maximum clinical dose in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139 times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose).

Nursing Mothers It is not known if EMPAGLIFLOZIN is excreted in human milk. Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from EMPAGLIFLOZIN, a decision should be made whether to discontinue nursing or to discontinue EMPAGLIFLOZIN, taking into account the importance of the drug to the mother.

Pediatric Use The safety and effectiveness of EMPAGLIFLOZIN in pediatric patients under 18 years of age have not been established.

Geriatric Use No EMPAGLIFLOZIN dosage change is recommended based on age. A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. EMPAGLIFLOZIN is expected to have diminished efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, EMPAGLIFLOZIN 10 mg, and EMPAGLIFLOZIN 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to

10.5%, 15.7%, and 15.1% in patients randomized to placebo, EMPAGLIFLOZIN 10 mg, and EMPAGLIFLOZIN 25 mg, respectively.

Renal Impairment The efficacy and safety of EMPAGLIFLOZIN were evaluated in a study of patients with mild and moderate renal impairment. In this study, 195 patients exposed to EMPAGLIFLOZIN had an eGFR between 60 and 90 mL/min/1.73 m2, 91 patients exposed to EMPAGLIFLOZIN had an eGFR between 45 and 60 mL/min/1.73 m2 and 97 patients exposed to EMPAGLIFLOZIN had an eGFR between 30 and 45 mL/min/1.73 m2 . The glucose lowering benefit of EMPAGLIFLOZIN25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

The efficacy and safety of EMPAGLIFLOZIN have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. EMPAGLIFLOZIN is not expected to be effective in these patient populations.

Hepatic Impairment EMPAGLIFLOZIN may be used in patients with hepatic impairment.

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. Adverse Reactions:

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension
- Impairment in Renal Function
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Genital Mycotic Infections
- Urinary Tract Infections [see Warnings and Precautions
- Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Trials evaluating EMPAGLIFLOZIN10 and 25 mg

The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. EMPAGLIFLOZIN was used as monotherapy in one trial and as add-on therapy in four trials.

These data reflect exposure of 1976 patients to EMPAGLIFLOZIN with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), EMPAGLIFLOZIN10 mg (N=999), or EMPAGLIFLOZIN25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular

complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m2).

Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of EMPAGLIFLOZIN. The adverse reactions were not present at baseline, occurred more commonly on EMPAGLIFLOZIN than on placebo and occurred in greater than or equal to 2% of patients treated with EMPAGLIFLOZIN 10 mg or EMPAGLIFLOZIN 25 mg.

Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with EMPAGLIFLOZIN and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of EMPAGLIFLOZIN Monotherapy or Combination Therapy

	Number (%) of Patients		
	Placebo N=995	EMPAGLIFLOZIN10 mg N=999	EMPAGLIFLOZIN25 mg N=977
Urinary tract infection[a]	7.6%	9.3%	7.6%
Female genital mycotic infections[b]	1.5%	5.4%	6.4%
Upper respiratory tract infection	3.8%	3.1%	4.0%
Increased urination[c]	1.0%	3.4%	3.2%
Dyslipidemia	3.4%	3.9%	2.9%
Arthralgia	2.2%	2.4%	2.3%
Male genital mycotic infections[d]	0.4%	3.1%	1.6%
Nausea	1.4%	2.3%	1.1%

a Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis.
b Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), EMPAGLIFLOZIN10 mg (N=443), EMPAGLIFLOZIN25 mg (N=420).
c Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia d Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), EMPAGLIFLOZIN10 mg (N=556), EMPAGLIFLOZIN25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, EMPAGLIFLOZIN10 mg, and EMPAGLIFLOZIN25 mg, respectively.
Volume Depletion EMPAGLIFLOZIN causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion

(e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, EMPAGLIFLOZIN10 mg, and EMPAGLIFLOZIN25 mg respectively. EMPAGLIFLOZIN may increase the risk of hypotension in patients at risk for volume contraction.

Increased Urination In the pool five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on EMPAGLIFLOZIN than on placebo (see Table 1). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, EMPAGLIFLOZIN10 mg, and EMPAGLIFLOZIN25 mg, respectively.

Impairment in Renal Function Use of EMPAGLIFLOZINwas associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes.

Table 2 Changes from Baseline in Serum Creatinine and eGFR in the Pool of Four 24-week Placebo-Controlled Studies and Renal Impairment Study

		Pool of 24-Week Placebo-Controlled Studies		
		Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
Baseline Mean	N	825	830	822
	Creatinine (mg/dL)	0.84	0.85	0.85
	eGFR (mL/min/1.73 m^2)	87.3	87.1	87.8
Week 12 Change	N	771	797	783
	Creatinine (mg/dL)	0.00	0.02	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-1.3	-1.4
Week 24 Change	N	708	769	754
	Creatinine (mg/dL)	0.00	0.01	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-0.6	-1.4
		Moderate Renal Impairment*		
		Placebo		JARDIANCE 25 mg
Baseline	N	187	--	187
	Creatinine (mg/dL)	1.49	--	1.46
	eGFR (mL/min/1.73 m2)	44.3	--	45.4
Week 12 Change	N	176	--	179
	Creatinine (mg/dL)	0.01	--	0.12
	eGFR (mL/min/1.73 m^2)	0.1	--	-3.8
Week 24 Change	N	170	--	171
	Creatinine (mg/dL)	0.01	--	0.10
	eGFR (mL/min/1.73 m^2)	0.2	--	-3.2
Week 52 Change	N	164	--	162
	Creatinine (mg/dL)	0.02	--	0.11
	eGFR (mL/min/1.73 m^2)	-0.3	--	-2.8

*Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2

Hypoglycemia The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when EMPAGLIFLOZINwas administered with insulin or sulfonylurea.

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Controlled Clinical Studies

Monotherapy (24 weeks)	**Placebo (n=229)**	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 25 mg (n=223)**
Overall (%)	0.4%	0.4%	0.4%
Severe (%)	0%	0%	0%
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**JARDIANCE 10 mg + Metformin (n=217)**	**JARDIANCE 25 mg + Metformin (n=214)**
Overall (%)	0.5%	1.8%	1.4%
Severe (%)	0%	0%	0%
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)**	**JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4%	16.1%	11.5%
Severe (%)	0%	0%	0%
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)**	**JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8%	1.2%	2.4%
Severe (%)	0%	0%	0%
In Combination with Insulin (18 weeks[c])	**Placebo (n=170)**	**JARDIANCE 10 mg (n=169)**	**JARDIANCE 25 mg (n=155)**
Overall (%)	20.6%	19.5%	28.4%
Severe (%)	0%	0%	1.3%

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections In the pool five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with EMPAGLIFLOZIN compared to placebo, occurring in 0.9%, 4.1%. and 3.7% of patients randomized to placebo, EMPAGLIFLOZIN10 mg, and EMPAGLIFLOZIN25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either EMPAGLIFLOZIN10 or 25 mg. Genital mycotic infections occurred more frequently in female than male patients (see Table 1). Phimosis occurred more frequently in male patients treated with EMPAGLIFLOZIN10 mg (less than 0.1%) and EMPAGLIFLOZIN25 mg (0.1%) than placebo (0%).

Urinary Tract Infections In the pool five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with EMPAGLIFLOZIN compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, EMPAGLIFLOZIN 10 mg, and EMPAGLIFLOZIN 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, EMPAGLIFLOZIN 10 mg, and EMPAGLIFLOZIN 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, EMPAGLIFLOZIN 10 mg, and EMPAGLIFLOZIN 25 mg was 3.2%, 3.6%, and 4.1%, respectively.

Laboratory Tests

Increase in Low-Density Lipoprotein Cholesterol (LDL-C) Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with EMPAGLIFLOZIN. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, EMPAGLIFLOZIN 10 mg, and EMPAGLIFLOZIN 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in EMPAGLIFLOZIN 10 mg and 2.8% in EMPAGLIFLOZIN 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, EMPAGLIFLOZIN 10 mg, and EMPAGLIFLOZIN 25 mg, respectively.

4.9. Overdose

In the event of an overdose with EMPAGLIFLOZIN, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

4. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

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

Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Pharmacodynamic effects

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of EMPAGLIFLOZINand was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg EMPAGLIFLOZINonce daily.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment. In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology
In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of EMPAGLIFLOZIN25 mg, EMPAGLIFLOZIN200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

5.2 Pharmacokinetic properties
Absorption
The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 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 Cmax were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a doseproportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

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

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

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

Elimination
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Specific Populations

Renal Impairment

In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m2), and severe (eGFR: less than 30 mL/min/1.73 m2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Hepatic Impairment

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and Cmax increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Effects of Age, Body Mass Index, Gender, and Race

Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin in pediatric 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipient (s)

Xenglu 10mg tablets:

Core Materials:

Lactose 200 mesh
Avicel pH 101 microcrystalline cellulose
Croscarmellose Sodium
Hydroxy propyl cellulose
Aerosil 200 (silicon dioxide)
Magnesium Stearate
Deionized Water

Coated Material:

Hydroxy propyl methyl cellulose (HPMC Pharmacoat 606)
Titanium dioxide
Talcum powder
Polyethylene glycol-6000
Deionized Water

Xenglu 25mg tablets:
Core Materials:
Lactose 200 mesh
Avicel pH 101 microcrystalline cellulose
Croscarmellose Sodium
Hydroxy propyl cellulose
Aerosil 200 (silicon dioxide)
Magnesium Stearate
Deionized Water

Coated Material:
Hydroxy propyl methyl cellulose (HPMC Pharmacoat 606)
Titanium dioxide
Talcum powder
Polyethylene glycol-6000
Deionized Water

6.2. Incompatibilities

Un Known

6.3.Shelf - Life

2 years

6.4.Special precautions for storage

Store below 30°C. Protect from sunlight and moisture. Keep out of reach of children.

6.5.Nature and contents of container

Blister pack of printed Aluminium Foil with cold forming foil packed in printed carton along with leaflet.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Hilton Pharma (Pvt) Ltd.
8th & 9th Floor, Progressive Plaza, Beaumont
Road Karachi, Pakistan.

8. MARKETING AUTHORISATION NUMBER(S)

Xenglu 10mg Tablet
Registration # 093065

Xenglu 25mg Tablet
Registration # 093066

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of Registration: 16.01.2019

10. DATE OF THE REVISION OF THE TEXT

Not Applicable