SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

FORXIGA® 5 (Tablet)

FORXIGA® 10 (Tablet)

FORXIGA IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. FORXIGA IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES AND NOT INDICATED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT TYPE 2 DIABETES.

There have been reports of metabolic acidosis, including ketoacidosis, which were serious life-threatening or fatal, in patients taking FORXIGA.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 11 mmol/l. FORXIGA should be discontinued and the patient should be promptly evaluated and managed accordingly.

Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with FORXIGA.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. FORXIGA is contraindicated in these patients.

COMPOSITION:

FORXIGA 5:

Each tablet contains the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol.

Excipients: Crospovidone, lactose anhydrous, magnesium stearate, microcrystalline cellulose, hydrolysed polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and silicone dioxide.

Contains sugar: lactose anhydrous.

FORXIGA 10:

Each tablet contains the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol.

Excipients: Crospovidone, lactose anhydrous, magnesium stearate, microcrystalline cellulose, hydrolysed polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and silicone dioxide.

Contains sugar: lactose anhydrous.

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral hypoglycaemics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Dapagliflozin is a reversible inhibitor of sodium glucose co-transporter 2 (SGLT2). SGLT2 is selectively expressed in the kidney, and is the predominant transporter responsible for

reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycaemia in type 2 diabetes mellitus, reabsorption of filtered glucose continues. Dapagliflozin reduces both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24 hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

Urinary glucose excretion (glycosuria) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 3 000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

The urinary glucose excretion with dapagliflozin results in osmotic diuresis and increases in urinary volume. The increase in urinary volume may be associated with a transient increase in urinary sodium excretion that which may not be associated with changes in serum sodium concentrations.

Dapagliflozin may cause a decrease in systolic blood pressure and diastolic blood pressure.

Urinary uric acid excretion was also increased and accompanied by a reduction in serum uric acid concentration. At 24 weeks, changes in serum uric acid concentrations from baseline ranged from -0,0183 mmol/l to -0,0483 mmol/l.

Pharmacokinetic properties:

Absorption:

Dapagliflozin was absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50 % and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution:

Dapagliflozin is approximately 91 % protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment).

Metabolism:

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean

plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12,9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61 % of a 50 mg [^{14}C]-dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42 % [based on $AUC_{(0\text{-}12\ h)}$] of total plasma radioactivity, similar to the 39 % contribution by parent compound. No other metabolite accounted for > 5 % of the total plasma radioactivity at any time point measured. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP mediated metabolism was a minor clearance pathway in humans.

Elimination:

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2 % as unchanged dapagliflozin. After administration of 50 mg [^{14}C]-dapagliflozin dose, 96 % was recovered, 75 % in urine and 21 % in faeces. In faeces, approximately 15 % of the dose was excreted as parent compound.

Renal impairment:

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin that were 32 %, 60 % and 87 % higher, respectively, than those of patients with type 2 diabetes mellitus and normal renal function. At dapagliflozin 20 mg once daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24 hour glucose excretion. The renal glucose clearance and 24 hour glucose excretion was lower in patients with moderate or severe renal impairment as

compared to patients with normal and mild renal impairment. The steady-state 24 hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known. Dapagliflozin is contraindicated in patients whose GFR is less than 60 ml/min (see "Contraindications").

Hepatic impairment:

A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12 % and 36 % higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40 % and 67 % higher than matched healthy controls, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see "Warnings and Special Precautions").

Age:

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥ 18 to < 40 years [n = 105] and elderly: ≥ 65 years

[n = 224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥ 40 to < 65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10,4 % lower than in the reference group [90 % CI: 87,9; 92,2 %] and 25 % higher in elderly patients compared to the reference group [90 % CI: 123; 129 %]. These differences in systemic exposure were considered not to be clinically meaningful.

Paediatric and adolescent:

Pharmacokinetics in the paediatric and adolescent population have not been studied.

Body Weight:

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high body weight subjects (≥ 120 kg, n = 91) were estimated to be 78,3 % [90 % CI: 78,2; 83,2 %] of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥ 120 kg) is recommended.

Subjects with low body weights (< 50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29 % higher than subjects with the reference group body weight. This difference is considered to be small and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (< 50 kg) is recommended.

INDICATIONS:

FORXIGA is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

As an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Add-on combination therapy

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

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- Moderate and severe renal impairment with GFR < 60 ml/min, end stage renal failure or patients on dialysis.
- Diabetes Mellitus Type 1
- Pregnant women or women who are breast-feeding their infants (See “Pregnancy and Lactation”).

WARNINGS AND SPECIAL PRECAUTIONS:

General:

FORXIGA may cause a decrease in systolic blood pressure and diastolic blood pressure.

FORXIGA should not be used for the treatment of diabetic ketoacidosis.

Metabolic acidosis including ketoacidosis:

There have been postmarketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking FORXIGA. FORXIGA is contraindicated for the treatment of patients with type 1 diabetes mellitus (see "Contraindications").

Patients treated with FORXIGA who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 11 mmol/l (196 mg/dl). If ketoacidosis is suspected, FORXIGA should be discontinued and the patient should be promptly evaluated.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. FORXIGA is not indicated in these patients.

Use in patients with renal impairment:

The efficacy of FORXIGA is dependent on renal function (see "Contraindications"). Therefore, renal function should be monitored prior to initiation of FORXIGA and periodically thereafter (See "Dosage and Directions For Use").

Use in patients at risk for volume depletion:

The diuretic effect of FORXIGA is a potential concern for volume depleted patients. There is limited experience in clinical trials in patients at increased risk for volume depletion.

For patients at risk for volume depletion due to co-existing conditions or concomitant medicines, such as loop diuretics, a 5 mg starting dose of FORXIGA may be appropriate. FORXIGA should be permanently discontinued in patients who develop volume depletion (See "Side Effects").

Urinary tract infections:

Urinary tract infections were more frequently reported for FORXIGA compared to control in a placebo-pooled analysis up to 24 weeks. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of FORXIGA should be considered when treating pyelonephritis or urosepsis (See "Side Effects").

Treatment with FORXIGA increases the risk for urinary tract infections. There have been postmarketing reports of serious urinary tract infections, including pyelonephritis, requiring hospitalisation in patients receiving FORXIGA and other SGLT2 inhibitors. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Use with medicines known to cause hypoglycaemia:

Insulin and insulin secretagogues, such as sulfonylureas, cause 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 FORXIGA (See "Side Effects").

Paediatric use:

Safety and efficacy of FORXIGA in paediatric patients has not been established.

Other populations:

In general, patients with severe renal impairment (eGFR < 30 ml/min/1,73 m^2) or End Stage Renal Disease or with recent (< 2 months) cardiovascular event or heart failure New York Heart Association class IV or who are breast-feeding or are pregnant, have been excluded from clinical studies.

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. Patients must bear in mind the possibility of hypoglycaemia and its effects on their motor skills.

Lactose:

FORXIGA contain lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency, or glucose-galactose malabsorption should not FORXIGA.

INTERACTIONS:

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor. In *in-vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters.

The dependence of dapagliflozin elimination on dapagliflozin 3-O-glucuronide formation in humans also suggests the possibility of interactions mediated by UGT1A9. Ketoconazole is an *in vitro* inhibitors of dapagliflozin 3-O-glucuronide formation by UGT1A9 (IC50 = 32 μM).

Effects of other medicines on FORXIGA:

In studies conducted in healthy subjects, the pharmacokinetics of FORXIGA were not altered by metformin (a human OCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a human OAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an alpha-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). A 22 % decrease in dapagliflozin systemic exposure following co-administration with rifampicin was considered not to be large enough to warrant a dose adjustment.

Effect of FORXIGA on other medicines:

In studies conducted in healthy subjects, FORXIGA did not alter the pharmacokinetics of metformin (an hOCT 1 and hOCT 2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate)35, sitagliptin (a hOAT 3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide, valsartan, simvastatin (a CYP3A4 substrate), digoxin (a P gp substrate) or warfarin (S warfarin, a CYP2C19 substrate, R warfarin or the anticoagulatory effects of warfarin as measured by the prothrombin time [International Normalised Ratio (INR)]).

Other interactions:

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of FORXIGA have not been studied.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay:

Monitoring glycaemic control with 1,5-AG assay should not be used as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors, including FORXIGA. Use alternative methods to monitor glycaemic control.

PREGNANCY AND LACTATION:

Pregnancy:

FORXIGA is contraindicated in pregnancy. Maternal exposure to FORXIGA in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, FORXIGA should be discontinued (See "Contraindications").

Lactation:

Mothers on FORXIGA should not breast-feed their infants.

FORXIGA must not be used by a nursing woman. Studies in rats have shown excretion of FORXIGA in milk. Exposure to FORXIGA must be avoided during the first 2 years of life (See "Contraindications").

DOSAGE AND DIRECTIONS FOR USE:

Monotherapy and add-on combination therapy

The recommended dose is 10 mg FORXIGA once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin.

When FORXIGA is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Renal impairment:

No dosage adjustment for FORXIGA is indicated for mild renal impairment. The efficacy of FORXIGA is dependent on renal function. FORXIGA should not be used in patients with moderate to severe renal impairment (defined as eGFR < 60 ml/min/1,73 m^2 by MDRD or CrCl < 60 ml/min by Cockcroft-Gault) (See "Contraindications", "Warnings and Special Precautions" and "Side Effects").

Monitoring of renal function is recommended as follows:

- Prior to initiation of FORXIGA and at least annually, thereafter.
- Prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1,73 m^2, FORXIGA treatment should be discontinued.

Hepatic impairment:

No dosage adjustment for FORXIGA is necessary for patients with mild or moderate hepatic impairment. FORXIGA is not recommended for patients with severe hepatic impairment as efficacy has not been established (See "Pharmacokinetic Properties").

Patients at risk for volume depletion:

For patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, a 5 mg starting dose of FORXIGA may be appropriate (See

"Warnings and Special Precautions" and "Side Effects").

Elderly:

No dosage adjustment for FORXIGA is required based on age (See "Warnings and Special Precautions").

Paediatric and adolescent:

Safety and effectiveness of FORXIGA in paediatric and adolescent patients have not been established.

SIDE EFFECTS:

Clinical Experience:

A total of 6 228 patients with type 2 diabetes were randomised, including 4 287 patients treated with FORXIGA, in 14 double-blind, controlled, clinical safety and efficacy studies conducted to evaluate the effects of FORXIGA on glycaemic control. FORXIGA 10 mg was evaluated in 12 of these studies.

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10) and uncommon (≥ 1/1 000, < 1/100).

Table 1 Adverse reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies[a] reported in ≥ 2 % of patients treated with FORXIGA 10 mg and ≥ 1 % more frequently than in patients treated with placebo.

System organ class	**Very common**	**Common***	**Uncommon****

Infections and infestations		Vulvovaginitis, balanitis and related genital infections[b,c], Urinary tract infection[b,e], including pyelonephritis, cystitis.	Vulvovaginal pruritus
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion, dehydration, hypovolaemia, hypotension [b], Thirst[**]
Gastrointestinal Disorders			Constipation
Skin and subcutaneous tissue disorders		Rash	Hyperhidrosis
Musculoskeletal and connective tissue disorders		Back pain	
Renal and urinary disorders	Glucosuria	Dysuria, Polyuria[d]	Nocturia

Investigations		Dyslipidaemia[f], Haematocrit increased[g]	Blood creatinine Increased, Blood urea increased

[a] The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[b] See corresponding subsection below for additional information.

[c] Genital infection includes the preferred terms: Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess, balanoposthitis, genitourinary tract infection, penile abscess, posthitis.

[d] Polyuria includes the preferred terms: pollakiuria, polyuria, increased urine output, osmotic diuresis.

[e] Urinary tract infection includes the preferred terms: Escherichia urinary tract infection, genitourinary tract infection, trigonitis, urethritis, kidney infection, and prostatitis.

[f] Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 1,4 % versus -0 4 %; HDL cholesterol 5,5 % versus 3,8 %; LDL cholesterol 2,7 % versus -1,9 %; triglycerides -5,4 % versus -0,7 %.

[g] Mean changes from baseline in haematocrit were 2,30 % for dapagliflozin 10 mg versus – 0,33 % for placebo. Haematocrit values > 55 % were reported in 1,3 % of the subjects treated with dapagliflozin 10 mg versus 0,4 % of placebo subjects.

[*] Reported in ≥ 2 % of subjects and ≥ 1 % more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

** Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0,2 % of subjects and ≥ 0,1 % more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Additional adverse reactions in ≥ 5 % of patients treated with FORXIGA 10 mg, ≥ 1 % more than patients in placebo/comparator, and reported in at least 3 more patients treated with FORXIGA 10 mg and regardless of relationship to FORXIGA reported by investigator, are described below by treatment regimen.

- add-on to metformin studies: headache (5,3 % FORXIGA 10 mg and 3,1 % placebo).
- add-on to thiazolidinedione study: nasopharyngitis (7,9 % FORXIGA 10 mg and 3,6 % placebo), diarrhoea (6,4 % FORXIGA 10 mg and 4,3 % placebo).

In a study of patients with moderate renal impairment, a higher frequency of bone fractures was observed in groups treated with FORXIGA (8,2 %) compared with placebo (0 %) (See "Contraindications").

Volume depletion:

Events related to volume depletion (including reports of dehydration, hypovolaemia or hypotension) were reported in 0,7 %, 0,6 %, and 0,4 % of patients who received FORXIGA 10 mg, FORXIGA 5 mg and placebo, respectively, in the short-term, placebo-pooled analysis. Serious events occurred in ≤ 0,2 % of patients in the 14 clinical studies and were balanced between FORXIGA 10 mg, FORXIGA 5 mg and comparator (See "Warnings and Special Precautions").

In the following subgroups, the proportion of patients with events related to volume depletion for FORXIGA 10 mg, FORXIGA 5 mg and placebo were:

In patients who received loop diuretics: 2 patients (6,5 %), 0 patients, and 1 patient (1,8 %), respectively.

In patients ≥ 65 years of age: 2 patients (1,0 %), 1 patient (0,5 %) and 1 patient (0,4 %), respectively.

Genital infections:

Events of genital infections were reported in 4,8 % and 0,9 % of patients who received FORXIGA 10 mg and placebo, respectively, in the short-term, placebo-pooled analysis. Infections were more frequently reported in females (6,9 % FORXIGA 10 mg vs. 1,5 % placebo) than in males (2,7 % FORXIGA 10 mg vs. 0,3 % placebo).

Overall, treatment with FORXIGA 5 mg was similar to FORXIGA 10 mg treatment.

Urinary tract infections:

Events of urinary tract infections were reported in 4,3 % and 3,7 % of patients who received FORXIGA 10 mg and placebo, respectively, in the short term, placebo-pooled analysis. Infections were more frequently reported in females (7,7 % FORXIGA 10 mg vs. 6,6 % placebo) than in males (0,8 % FORXIGA 10 mg vs. 1 % placebo). (See “Warnings and Special Precautions”).

Hypoglycaemia:

The frequency of hypoglycaemia depended on the type of background therapy used in each study. Studies with add-on sulfonylurea and add-on insulin therapies had higher rates of hypoglycaemia. (See “Warnings and Special Precautions”).

In an add-on to glimepiride study up to 24 weeks, episodes of hypoglycaemia were reported in 10 (6,6 %) patients in the FORXIGA 10 mg plus glimepiride group and 3 (2,1 %) patients in the placebo plus glimepiride group.

In an add-on to insulin study up to 24 weeks, episodes of hypoglycaemia were reported in 79 (40,3 %) patients in the FORXIGA 10 mg plus insulin group and in 67 (34 %) patients in placebo plus insulin group. Patients in this study could also be treated with a maximum of 2 oral anti-diabetes medications (OADs) including metformin.

Decrease on blood pressure:

In the pool of 13 placebo-controlled studies, a decrease in blood pressure was observed in patients treated with FORXIGA 10 mg (mean seated systolic blood pressure change from baseline at Week 24 of −3,7 mmHg and mean seated diastolic blood pressure change of −1,8 mmHg for FORXIGA 10 mg vs −0,5 mmHg systolic and −0,5 mmHg diastolic blood pressure change for placebo group). Postural blood pressure measurement revealed orthostatic hypotension in 13,1 % of patients treated with FORXIGA 10 mg versus 11,3 % of patients treated with placebo over the 24-week treatment period. In addition, in 2 studies with patients with type 2 diabetes and hypertension, postural blood pressure measurement revealed orthostatic hypotension in 3,2 % of FORXIGA 10 mg-treated patients versus 1,7 % of placebo-treated patients across the 2 studies over the 12-week treatment period.

Laboratory findings:

Haematocrit:

A moderate increase in haematocrit occurs and may be an indication of volume depletion.

Serum inorganic phosphorous:

Increases from baseline in mean serum phosphorus levels were reported at Week 24 in FORXIGA 10 mg treated patients compared with placebo (mean increases of 0,0549 mmol/l vs. 0,0097 mmol/l, respectively). Similar results were seen at Week 50. Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥ 1,81 mmol/l if age 17-65 or ≥ 1,65 mmol/l if ≥ age 66) were reported in FORXIGA 10 mg group vs. placebo at Week 24 (1,7 % vs. 0,7 %, respectively) and during the short-term plus long-term phase (2,6 % vs. 1,5 %, respectively). The clinical relevance of these findings is unknown.

Lipids:

Changes from baseline in mean lipid values were reported at Week 24 in FORXIGA 10 mg treated patients compared with placebo. Mean percent change from baseline at Week 24 for FORXIGA 10 mg vs. placebo, respectively was as follows: total cholesterol 1,4 % vs. -0,4 %; HDL cholesterol 5,5 % vs. 3,8 %; LDL cholesterol 2,7 % vs. -1,9 %; triglycerides -5,4 % vs. 0,7 %. Mean percent change from baseline at Week 50 for FORXIGA 10 mg vs. placebo, respectively was as follows: total cholesterol 1,5 % vs. -0,7 %; HDL cholesterol 6,5 % vs. 2,5 %; LDL cholesterol 3,5 % vs. -0,7 %; triglycerides -3,9 % vs. 0,5 %. The ratio between LDL cholesterol and HDL cholesterol decreased for all treatment groups at Week 24.

Liver function tests:

In the placebo-pooled analysis, ALT > 3 x upper limit of normal (ULN) was reported in 0,8 % on FORXIGA 10 mg and 1,1 % on placebo over 24 weeks. In the overall clinical programme, ALT or AST > 3 x ULN and bilirubin > 2 x ULN was reported in 5 patients (0,1 %) on FORXIGA and 3 patients (0,2 %) on comparator. One patient receiving FORXIGA experienced a liver adverse event with diagnoses of drug induced hepatitis and autoimmune hepatitis.

Post-marketing adverse events:

Spontaneous reports:

Skin and sub-cutaneous tissue disorders: Rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, rash erythematous.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In overdose, side effects may be elicited or exacerbated. Appropriate symptomatic and supportive treatment should be initiated as dictated by the patient's clinical status. The removal of FORXIGA by haemodialysis has not been studied.

IDENTIFICATION:

FORXIGA 5:

Yellow, biconvex round, film-coated tablet with "5" debossed on one side and "1427" debossed on the other side.

FORXIGA 10:

Yellow, biconvex diamond, film-coated tablet with "10" debossed on one side and "1428" debossed on the other side.

PRESENTATION:

Silver aluminium/aluminium foil blister packs of 14, 28, 30, 90 and 98 tablets packed in a carton.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep out of reach of children. Store in the original package.

REGISTRATION NUMBER:

FORXIGA 5: 46/21.2/0214

FORXIGA 10: 46/21.2/0215

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date on registration certificate:

29 September 2017

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

FORXIGA® 5

FORXIGA® 10

Dapagliflozin 5 mg, Dapagliflozin 10 mg

Tablet

DO NOT USE FORXIGA IF YOU HAVE TYPE 1 DIABETES. FORXIGA MUST NOT BE USED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT TYPE 2 DIABETES.

There have been reports of metabolic acidosis, including ketoacidosis, in patients taking FORXIGA.

Metabolic acidosis is an imbalance of acids in your blood, shown on blood tests. It is a serious and sometimes fatal condition that requires hospitalisation. Risk factors for metabolic acidosis include sudden decrease of your insulin dose, prolonged fasting from food and drink, or increasing your insulin dose due to major surgery or serious illness, or alcohol abuse. Caution is advised when using FORXIGA if you have these conditions. Diabetic ketoacidosis is a type of metabolic acidosis. Diabetic ketoacidosis is an increase of ketone bodies in your blood or urine, shown on blood or urine tests. Risk factors for diabetic ketoacidosis include pancreatic conditions, such as inflammation of the pancreas or previous pancreatic surgery. Do not use FORXIGA if you have these conditions.

Metabolic acidosis, including diabetic ketoacidosis, may occur in patients with type 2 diabetes mellitus with normal (blood glucose test result below 11 mmol/l) or high blood sugar levels who are treated with FORXIGA.

Contact a doctor or the nearest hospital straight away if you have the following symptoms even if your blood sugar levels are normal: nausea, vomiting, abdominal pain, fatigue, thirst, passing of large volumes of urine, shortness of breath and confusion. These symptoms could be a sign of metabolic or diabetic ketoacidosis.

Read all of this leaflet carefully before you start taking FORXIGA.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- FORXIGA has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT FORXIGA CONTAINS:

The active substance is dapagliflozin.

Each FORXIGA 5 tablet contains 5 mg dapagliflozin

Each FORXIGA 10 tablet contains 10 mg dapagliflozin

The other ingredients are:

- Tablet core: crospovidone, lactose anhydrous, magnesium stearate, microcrystalline cellulose, silicon dioxide,
- Film-coating: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide

Contains sugar: lactose

2. WHAT FORXIGA IS USED FOR:

- FORXIGA is used if your type 2 diabetes cannot be controlled with different medicines for diabetes, diet and exercise.

- Your doctor may ask you to take FORXIGA alone or with another diabetes medicines.

- FORXIGA increases the amount of sugar excreted by your kidneys.

FORXIGA is not recommended for children and young people under 18 years.

It is important to keep following the advice about diet and exercise given to you by your doctor, nurse or pharmacist.

3. BEFORE YOU TAKE FORXIGA:

Do not take FORXIGA if:

- you are allergic (hypersensitive) to dapagliflozin or any of the other ingredients of FORXIGA (listed in Section 1, "What FORXIGA contains"). If you are not sure, talk to your doctor or pharmacist before taking this medicine.

- you have moderate or severe kidney disease or you are on dialysis.

- you have type 1 diabetes – the type that usually starts when you are young, and your body does not produce any insulin.

- you are pregnant or plan to become pregnant. Talk with your doctor about the best way to control your blood sugar while you are pregnant.

- you are breast-feeding. Talk to your doctor if you would like to breast-feed.

Take special care with FORXIGA:

Check with your doctor or pharmacist:

- if you are going to have surgery
- if you are eating less due to illness or surgery, or you are dieting
- if you have or have had problems with your pancreas
- if you drink large amounts of alcohol, either every day or only from time to time
- if you develop any of the following symptoms, which may be signs of ketoacidosis: nausea, vomiting, stomach-area (abdominal) pain, tiredness, trouble breathing, increased levels of "ketone bodies" in your urine or blood. If this happens to you contact a doctor or the nearest hospital immediately.
- if you have mild kidney disease your doctor will want to monitor your kidney function on an ongoing basis.
- if you are on medicines to lower your blood pressure (anti-hypertensives) or water pill (diuretic) and have a history of low blood pressure (hypotension).
- if you often get infections of the urinary tract.
- if you are allergic to any other medicine used to lower the amount of sugar in your blood.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking FORXIGA.

Pregnancy and Breast-feeding:

You should not take FORXIGA if you are pregnant or breast-feeding your baby. If you are pregnant or breast-feeding, please consult your doctor, pharmacist or other healthcare professional for advice before taking/ receiving FORXIGA.

Driving and using machinery:

Taking FORXIGA with other medicines or insulin used to treat your diabetes can cause too low blood sugar levels (hypoglycaemia), which may cause symptoms such as shaking, sweating and change in vision, and may affect your ability to drive and use machines. Do not drive or use any tools or machines, if you feel dizzy while taking FORXIGA.

Important information about some of the ingredients of FORXIGA:

FORXIGA contains lactose. Patients with the rare hereditary conditions of lactose or galactose intolerance should not take FORXIGA.

Taking other medicines with FORXIGA:

If you are taking other medicine on a regular basis, including complementary or traditional medicine, the use of FORXIGA with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice.

Tell your doctor if:

- you are taking ketoconazole (medication for fungal infections).
- you are taking a water pill (diuretic) – you may be more likely to lose fluid from your body (get dehydrated). Your doctor may change your dose. Possible signs of losing too much fluid from your body are listed in Section 5 “Possible Side Effects”.
- you are taking other medicines that lower the amount of sugar in your blood - such as insulin or a “sulphonylurea” medicine. Your doctor may want to lower your dose of these other medicines, to stop you from getting low blood sugar (hypoglycaemia).

4. HOW TO TAKE FORXIGA:

Do not share medicines prescribed for you with any other person.

Always take FORXIGA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

How much to take

- The usual dose is one 10 mg tablet each day.
- Your doctor will prescribe the strength that is right for you.
- Your doctor will tell you how long your treatment with FORXIGA will last.
- Do not stop treatment early.
- If you have the impression that the effect of FORXIGA is too strong or too weak, tell your doctor or pharmacist.

Taking this medicine

- Swallow the tablet whole with some water.
- You can take your tablet with or without food.
- You can take the tablet at any time of the day. However, try to take it at the same time each day. This will help you to remember to take it.

Your doctor may prescribe FORXIGA together with other medicines to lower the amount of sugar in your blood.

Use in children:

FORXIGA is not recommended for children or young people under 18 years old.

Diet and exercise

To control your diabetes, you still need to diet and exercise, even when you are taking this medicine. So, it is important to keep following the advice about diet and exercise from your health care professional. In particular, if you are following a diabetic weight control diet, keep on with this while you are taking FORXIGA.

If you take more FORXIGA than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take FORXIGA:

Take your missed dose as soon as you remember, if within a few hours after missing a dose. However, if it is nearly time for your next dose, skip the missed dose. Then take your next dose at the usual time. Do not take a double dose to make up for forgotten individual doses.

Effects when treatment with FORXIGA is stopped:

Do not stop taking FORXIGA without talking to your doctor first. If you have the impression that the effect of FORXIGA is too strong or too weak, talk to your doctor or pharmacist.

5. POSSIBLE SIDE EFFECTS:

Diabetic ketoacidosis (diabetic coma) and similar side effects may occur. Symptoms are nausea, vomiting, abdominal pain, fatigue, thirst, passing of large volumes of urine, shortness of breath and mental confusion. Urgent medical attention is required.

FORXIGA can have side effects. Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

If you have a hypersensitivity (allergic) reaction, stop taking FORXIGA and tell your doctor immediately or go to the casualty department at your nearest hospital.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- very dry or sticky mouth, feeling very thirsty
- feeling very sleepy or tired
- passing little or no water (urine)
- fast heart beat

  These are signs of losing too much fluid from your body (volume depletion or dehydration).

- fever or chills
- burning sensation when passing water (urinating)
- pain in your back or side
- blood in your urine, although uncommon

  These are signs of a severe infection of the urinary tract.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

The following side effects have been frequently reported:

- low blood sugar levels (hypoglycaemia) - when taking this medicine with other medication or insulin to treat your diabetes.

  These are signs of low blood sugar (hypoglycaemia):

  - shaking, sweating, feeling very anxious, fast heart beat

  - feeling hungry, headache, change in vision

  - a change in your mood or feeling confused.

  Your doctor will tell you how to treat low blood sugar and what to do if you get any of the signs above.

- yeast infection (thrush) of your penis or vagina

- back pain

- passing more water (urine) than usual or needing to pass water more often

- high sugar levels (glucose) in urine (shown in tests).

- changes in the amount of cholesterol or fats in your blood (shown in tests)

- broken bones, if you already have moderate kidney problems.

- changes in the amount of red blood cells in your blood (shown in tests).

- infection of the bladder

- headache – when taking FORXIGA with metformin

- sore throat or diarrhoea – when taking FORXIGA with pioglitazone.

- rash

The following side effects have been reported less frequently:

- awakening from sleep at night to pass urine
- change in amount of creatinine cleared from blood (shown in tests).
- change in amount of urea in blood (shown in tests).
- increase thirst and dry feeling of the mouth
- constipation
- itching of the genitals
- increase sweating

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

6. STORING AND DISPOSING OF FORXIGA:

Store at or below 30 °C. Store in the original package.

Do not use FORXIGA after the expiry date stated on the container.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

7. PRESENTATION OF FORXIGA:

Silver aluminium/aluminium foil blister packs of 14, 28, 30, 90 and 98 tablets packed in a carton.

Not all pack sizes may be marketed.

8. IDENTIFICATION OF FORXIGA:

FORXIGA 5:

Yellow, biconvex round, film-coated tablet with "5" debossed on one side and "1427" debossed on the other side.

FORXIGA 10:

Yellow, biconvex diamond, film-coated tablet with "10" debossed on one side and "1428" debossed on the other side.

9. REGISTRATION NUMBERS:

FORXIGA 5: 46/21.2/0214

FORXIGA 10: 46/21.2/0215

10. NAME AND ADDRESS OF REGISTRATION HOLDER:

AstraZeneca Pharmaceuticals (Pty) Limited

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2191

11. DATE OF PUBLICATION:

Date on registration certificate:

29 September 2017