ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

Excipient with known effect:
Each tablet contains 25 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, biconvex, 0.7 cm diameter round, film-coated tablets with "5" engraved on one side and "1427" engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology
Monotherapy and add-on combination therapy
The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. When dapagliflozin 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 (see sections 4.5 and 4.8).

Special populations
Renal impairment
The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2, see sections 4.4, 4.8, 5.1 and 5.2).

No dosage adjustment is indicated in patients with mild renal impairment.

Hepatic impairment
No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg (see sections 4.4 and 5.2).

Elderly (≥ 65 years)
In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 5.2). Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.

Paediatric population
The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Method of administration
Forxiga can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Forxiga should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Use in patients with renal impairment
The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2). Forxiga has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m^2) or end-stage renal disease (ESRD).

Monitoring of renal function is recommended as follows:
• Prior to initiation of dapagliflozin and at least yearly, thereafter (see sections 4.2, 4.8, 5.1 and 5.2)
• Prior to initiation of concomitant medicinal products 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, dapagliflozin treatment should be discontinued.

Use in patients with hepatic impairment
There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances
Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure (see section 5.1), which may be more pronounced in patients with very high blood glucose concentrations.

Dapagliflozin is not recommended for use in patients receiving loop diuretics (see section 4.5) or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).

Caution should be exercised in patients for whom a dapagliflozin-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 elderly patients.

For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Urinary tract infections
Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo in a pooled analysis up to 24 weeks (see section 4.8). Pyelonephritis was uncommon and occurred at a similar frequency to control. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis.

Elderly patients
Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see sections 4.2, 4.4, 4.8 and 5.1).

In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible (see section 4.8).

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion (see section 4.8).

Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended (see sections 4.2 and 5.2).

Cardiac failure
Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

Use in patients treated with pioglitazone
While a causal relationship between dapagliflozin and bladder cancer is unlikely (see sections 4.8 and 5.3), as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.

Elevated haematocrit
Haematocrit increase was observed with dapagliflozin treatment (see section 4.8); therefore, caution in patients with already elevated haematocrit is warranted.

Combinations not studied
Dapagliflozin has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon-like peptide 1 (GLP-1) analogues.

Urine laboratory assessments
Due to its mechanism of action, patients taking Forxiga will test positive for glucose in their urine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Diuretics
Dapagliflozin may add to the diuretic effect of thiazide 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, 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 dapagliflozin (see sections 4.2 and 4.8).

Pharmacokinetic interactions
The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin
Interaction studies conducted in healthy subjects, using mainly a single dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products
In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant**.**

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

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 5.3). Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy.

When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Breast-feeding
It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring (see section 5.3). A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Fertility
The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

4.7 Effects on ability to drive and use machines

Forxiga has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile
In a pre-specified pooled analysis of 12 placebo-controlled studies, 1,193 subjects were treated with dapagliflozin 10 mg and 1,393 were treated with placebo.

The overall incidence of adverse events (short-term treatment) in subjects treated with dapagliflozin 10 mg was similar to placebo. Few adverse events led to discontinuation of treatment and were balanced across study groups. The most commonly reported events leading to discontinuation in patients treated with dapagliflozin 10 mg were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%). One subject receiving dapagliflozin experienced a liver adverse event with diagnoses of drug induced hepatitis and/or autoimmune hepatitis.

The most frequently reported adverse reaction was hypoglycaemia, which depended on the type of background therapy used in each study. The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add-on sulphonylurea (SU) and add-on insulin therapies. Combination therapies with sulphonylurea and add-on insulin had higher rates of hypoglycaemia (see *Hypoglycaemia* below).

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical trials. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse reactions in placebo-controlled studies[a]

System organ class	**Very common**	**Common***	**Uncommon****
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[b,c] Urinary tract infection[b]	Vulvovaginal pruritus
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst
Gastrointestinal disorders			Constipation
Skin and subcutaneous tissue disorders			Hyperhidrosis
Musculoskeletal and connective tissue disorders		Back pain	
Renal and urinary disorders		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]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.
[d]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.
[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.
[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 2.15% for dapagliflozin 10 mg versus -0.40% for placebo.
*Reported in ≥ 2% of subjects treated with dapagliflozin 10 mg and ≥ 1% more frequently than placebo.
**Reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg regardless of glycaemic rescue compared to placebo.

Description of selected adverse reactions

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in each study.

The frequency of minor episodes of hypoglycaemia was similar (< 4%) between treatment groups, including placebo. Across all studies, major events of hypoglycaemia were uncommon and

comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add on insulin therapies had higher rates of hypoglycaemia (see section 4.5).

In an add-on to glimepiride study, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0%) than in the placebo plus glimepiride group (2.1%).

In an add-on to insulin study, minor episodes were reported more frequently in the group treated with dapagliflozin 10 mg plus insulin (40.3%) than in the placebo plus insulin group (34.0%).

Volume depletion
Reactions related to volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 0.8% and 0.4% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo (see section 4.4).

Vulvovaginitis, balanitis and related genital infections
Vulvovaginitis, balanitis and related genital infections were reported in 4.8% and 0.9% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (9.7% and 3.4% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

Urinary tract infections
Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.3% versus 3.7%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

Parathyroid hormone (PTH)
Small increases in serum PTH levels were observed with increases being larger in subjects with higher baseline PTH concentrations. Bone mineral density measurements in patients with normal or mildly impaired renal function did not indicate bone loss over a treatment period of one year.

Malignancies
During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.

Special populations
Elderly patients (≥ 65 years)
In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 2.5% of subjects treated with dapagliflozin and 1.1% of subjects treated with placebo (see section 4.4). The most commonly reported adverse reaction related to renal function was increased serum creatinine. The majority of these reactions were transient and reversible. In subjects ≥ 65 years of age, adverse reactions of volume depletion, most commonly reported as hypotension, were reported in

1.5% and 0.4% of dapagliflozin-treated subjects and placebo-treated subjects, respectively (see section 4.4).

4.9 Overdose

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Other blood glucose lowering drugs, excluding insulins, ATC code: A10BX09

Mechanism of action
Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2).

The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 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, reabsorption of filtered glucose continues. Dapagliflozin improves 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 GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with Forxiga.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. 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 > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects
Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 ml/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/l (-0.87 to -0.33 mg/dl).

Clinical efficacy and safety
Eleven double-blind, randomised, controlled clinical trials were conducted with 5,693 subjects with type 2 diabetes to evaluate the efficacy and safety of Forxiga; 3,939 subjects in these studies were treated with dapagliflozin. Ten studies had a treatment period of 24 weeks duration, 5 with long-term extensions ranging from 24 to 78 weeks (up to a total study duration of 102 weeks), and one study was 52 weeks in duration. Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty-one percent had mild renal impairment and 12% had moderate renal impairment. Fifty-one percent (51%) of the subjects were men, 84% were White, 10% were Asian, 3% were Black and 3% were of other racial groups. Eighty percent (80%) of the subjects had a body mass index (BMI) ≥ 27.

Glycaemic control
Monotherapy
A double-blind, placebo-controlled study of 24-week duration (with an additional extension period) was conducted to evaluate the safety and efficacy of monotherapy with Forxiga in subjects with inadequately controlled type 2 diabetes mellitus. Once-daily treatment with dapagliflozin resulted in statistically significant ($p < 0.0001$) reductions in HbA1c compared to placebo (Table 2).

In the extension period, HbA1c reductions were sustained through Week 102 (-0.63%, and -0.18% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively).

Table 2. Results at Week 24 (LOCF[a]) of a placebo-controlled study of dapagliflozin as monotherapy

	Monotherapy	
	Dapagliflozin 10 mg	**Placebo**
N[b]	70	75
HbA1c (%)		
Baseline (mean)	8.01	7.79
Change from baseline[c]	-0.89	-0.23
Difference from placebo[c]	-0.66[*]	
(95% CI)	(-0.96, -0.36)	
Subjects (%) achieving: HbA1c < 7%		
Adjusted for baseline	50.8[§]	31.6
Body weight (kg)		
Baseline (mean)	94.13	88.77
Change from baseline[c]	-3.16	-2.19
Difference from placebo[c]	-0.97	
(95% CI)	(-2.20, 0.25)	

[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward
[b]All randomised subjects who took at least one dose of double-blind study medication during the short-term double-blind period
[c]Least squares mean adjusted for baseline value
[*]p-value < 0.0001 versus placebo
[§] Not evaluated for statistical significance as a result of the sequential testing procedure for secondary end points

Combination therapy
In a 52-week, active-controlled non-inferiority study, Forxiga was evaluated as add-on therapy to metformin compared with a sulphonylurea (glipizide) as add-on therapy to metformin in subjects with inadequate glycaemic control (HbA1c > 6.5% and ≤ 10%). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared to glipizide, thus demonstrating non-inferiority (Table 3). A significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%) experienced at least one event of hypoglycaemia over 52 weeks of treatment compared to the group treated with glipizide (40.8%).

Table 3. Results at Week 52 (LOCF[a]) in an active-controlled study comparing dapagliflozin to glipizide as add-on to metformin

Parameter	**Dapagliflozin + metformin**	**Glipizide + metformin**
N[b]	400	401
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline[c]	-0.52	-0.52
Difference from glipizide + metformin[c] (95% CI)	0.00[d] (-0.11, 0.11)	
Body weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline[c]	-3.22	1.44
Difference from glipizide + metformin[c] (95% CI)	-4.65[*] (-5.14, -4.17)	

[a]LOCF: Last observation carried forward
[b]Randomised and treated subjects with baseline and at least 1 post-baseline efficacy measurement
[c]Least squares mean adjusted for baseline value
[d]Non-inferior to glipizide + metformin
[*]p-value < 0.0001

Dapagliflozin as an add-on with either metformin, glimepiride or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p < 0.0001$; Tables 4 and 5).

Based on longitudinal repeated measures analysis, excluding data after rescue, the reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data. In addition, for the add-on to metformin study, HbA1c reductions were sustained through Week 102 (-0.78% and 0.02% adjusted mean change from baseline for 10 mg and placebo, respectively).

Table 4. Results of 24-week (LOCF[a]) placebo-controlled studies of dapagliflozin in add-on combination with metformin or glimepiride

	Add-on combination			
	Metformin[1]		**Sulphonylurea (glimepiride[2])**	
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
N[b]	135	137	151	145
HbA1c (%)				
Baseline (mean)	7.92	8.11	8.07	8.15
Change from baseline[c]	-0.84	-0.30	-0.82	-0.13
Difference from placebo[c]	-0.54*		-0.68*	
(95% CI)	(-0.74, -0.34)		(-0.86, -0.51)	
Subjects (%) achieving: HbA1c < 7%				
Adjusted for baseline	40.6**	25.9	31.7*	13.0
Body weight (kg)				
Baseline (mean)	86.28	87.74	80.56	80.94
Change from baseline[c]	-2.86	-0.89	-2.26	-0.72
Difference from placebo[c]	-1.97*		-1.54*	
(95% CI)	(-2.63, -1.31)		(-2.17, -0.92)	

[1]Metformin ≥ 1500 mg/day; [2]glimepiride 4 mg/day

[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

[c]Least squares mean adjusted for baseline value

*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product

**p-value < 0.05 versus placebo + oral glucose-lowering medicinal product

Table 5. Results at Week 24 (LOCF[a]) in a placebo-controlled study of dapagliflozin in combination with insulin (alone or with oral glucose-lowering medicinal products)

Parameter	Dapagliflozin 10 mg + insulin ± oral glucose-lowering medicinal products[2]	Placebo + insulin ± oral glucose-lowering medicinal products[2]
N[b]	194	193
HbA1c (%)		
Baseline (mean)	8.58	8.46
Change from baseline[c]	-0.90	-0.30
Difference from placebo[c]	-0.60[*]	
(95% CI)	(-0.74, -0.45)	
Body weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline[c]	-1.67	0.02
Difference from placebo[c]	-1.68[*]	
(95% CI)	(-2.19, -1.18)	
Mean daily insulin dose (IU)[1]		
Baseline (mean)	77.96	73.96
Change from baseline[c]	-1.16	5.08
Difference from placebo[c]	-6.23[*]	
(95% CI)	(-8.84, -3.63)	
Subjects with mean daily insulin dose reduction of at least 10% (%)	19.6[**]	11.0

[a]LOCF: Last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

[c]Least squares mean adjusted for baseline value and presence of oral glucose-lowering medicinal product

[*]p-value < 0.0001 versus placebo + insulin ± oral glucose-lowering medicinal product

[**]p-value < 0.05 versus placebo + insulin ± oral glucose-lowering medicinal product

[1]Up-titration of insulin regimens (including short-acting, intermediate, and basal insulin) was only allowed if subjects met pre-defined FPG criteria.

[2]Fifty percent of subjects were on insulin monotherapy at baseline; 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group, 80% were on metformin alone, 12% were on metformin plus sulphonylurea therapy, and the rest were on other oral glucose-lowering medicinal products.

Fasting plasma glucose

Treatment with dapagliflozin 10 mg as a monotherapy or as an add-on to either metformin, glimepiride or insulin resulted in statistically significant reductions in fasting plasma glucose (-1.64 to -1.20 mmol/l [-29.6 to -21.7 mg/dl]) compared to placebo (-0.33 to 0.18 mmol/l [-6.0 to 3.3 mg/dl]). This effect was observed at Week 1 of treatment and maintained in studies extended through Week 102.

Post-prandial glucose

Treatment with dapagliflozin 10 mg as an add-on to glimepiride resulted in statistically significant reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Body weight

Dapagliflozin 10 mg as an add-on to metformin, glimepiride or insulin resulted in statistically significant body weight reduction at 24 weeks. In longer-term trials, when added to metformin, these effects were sustained at 52 weeks (-4.65 kg reduction versus glipizide) and 102 weeks (-3.07 kg reduction versus placebo).

A 24-week study in 182 diabetic subjects using dual energy X-ray absorptiometry (DXA) to evaluate body composition demonstrated reductions with dapagliflozin 10 mg plus metformin compared with placebo plus metformin, respectively, in body weight and body fat mass as measured by DXA rather than lean tissue or fluid loss. Treatment with Forxiga plus metformin showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment in a magnetic resonance imaging substudy.

Blood pressure
In a pre-specified pooled analysis of 12 placebo-controlled studies, treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of -4.4 mmHg and diastolic blood pressure of -2.1 mmHg versus -0.9 mmHg systolic and -0.5 mmHg diastolic blood pressure for placebo group at Week 24.

Cardiovascular safety
A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 36.6% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 70.0% had hypertension. Cardiovascular episodes were adjudicated by an independent adjudication committee. The primary end point was the time-to-first event of one of the following outcomes: cardiovascular death, stroke, myocardial infarction (MI) or hospitalisation for unstable angina. Primary episodes occurred at a rate of 1.64% per patient-year in subjects treated with dapagliflozin and 1.99% in comparator-treatment subjects, per patient-year. The hazard ratio comparing dapagliflozin to comparator was 0.82 (95% Confidence interval [CI]: 0.58, 1.15), indicating that in this analysis Forxiga is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI and stroke were observed with a hazard ratio of 0.79 (95% CI: 0.54, 1.17).

Patients with renal impairment
Moderate renal impairment (eGFR ≥ 30 to < 60 ml/min/1.73 m^2)
The efficacy of dapagliflozin was also assessed separately in a dedicated study of diabetic subjects with moderate renal impairment (252 subjects with mean eGFR 44 ml/min/1.73 m^2). The mean change from baseline in HbA1c at 24 weeks was -0.44% and -0.32%, for dapagliflozin 10 mg and placebo, respectively.

Patients with baseline HbA1c ≥ 9%
In a pre-specified analysis of subjects with baseline HbA1c ≥ 9.0%, treatment with dapagliflozin 10 mg resulted in statistically significant reductions in HbA1c at Week 24 as a monotherapy (adjusted mean change from baseline: -2.04% and 0.19% for dapagliflozin 10 mg and placebo, respectively) and as an add-on to metformin (adjusted mean change from baseline: -1.32% and -0.53% for dapagliflozin and placebo, respectively).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with dapagliflozin in one or more subsets of the paediatric population in the treatment of type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC_{τ} values following once daily 10 mg doses of dapagliflozin were 158 ng/ml and 628 ng h/ml, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. 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. Hence, Forxiga can be administered with or without food.

Distribution
Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 l.

Biotransformation
Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. 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
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. The mean total systemic clearance of dapagliflozin administered intravenously was 207 ml/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [^{14}C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Linearity
Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Special populations
Renal impairment
At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. 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 subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on dapagliflozin exposure is not known.

Hepatic impairment
In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), 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. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Elderly patients (≥ 65 years)
There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Paediatric population
Pharmacokinetics in the paediatric population have not been studied.

Gender
The mean dapagliflozin AUC_{ss} in females was estimated to be about 22% higher than in males.

Race
There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight
Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Reproductive and developmental toxicity
Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed *in utero* and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460i)
Lactose, anhydrous
Crospovidone (E1201)
Silicon dioxide (E551)
Magnesium stearate (E470b)

Film-coating
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/Alu blister
Pack sizes of 14, 28 and 98 film-coated tablets in non-perforated calendar blisters
Pack sizes of 30x1 and 90x1 film-coated tablets in perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

Excipient with known effect:
Each tablet contains 50 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, biconvex, approximately 1.1 x 0.8 cm diagonally diamond-shaped, film-coated tablets with "10" engraved on one side and "1428" engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology
Monotherapy and add-on combination therapy
The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. When dapagliflozin 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 (see sections 4.5 and 4.8).

Special populations
Renal impairment
The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2, see sections 4.4, 4.8, 5.1 and 5.2).

No dosage adjustment is indicated in patients with mild renal impairment.

Hepatic impairment
No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg (see sections 4.4 and 5.2).

Elderly (≥ 65 years)
In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 5.2). Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.

Paediatric population
The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Method of administration
Forxiga can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Forxiga should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Use in patients with renal impairment
The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2). Forxiga has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m^2) or end-stage renal disease (ESRD).

Monitoring of renal function is recommended as follows:
• Prior to initiation of dapagliflozin and at least yearly, thereafter (see sections 4.2, 4.8, 5.1 and 5.2)
• Prior to initiation of concomitant medicinal products 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, dapagliflozin treatment should be discontinued.

Use in patients with hepatic impairment
There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances
Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure (see section 5.1), which may be more pronounced in patients with very high blood glucose concentrations.

Dapagliflozin is not recommended for use in patients receiving loop diuretics (see section 4.5) or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).

Caution should be exercised in patients for whom a dapagliflozin-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 elderly patients.

For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Urinary tract infections
Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo in a pooled analysis up to 24 weeks (see section 4.8). Pyelonephritis was uncommon and occurred at a similar frequency to control. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis.

Elderly patients
Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see sections 4.2, 4.4, 4.8 and 5.1).

In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible (see section 4.8).

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion (see section 4.8).

Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended (see sections 4.2 and 5.2).

Cardiac failure
Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

Use in patients treated with pioglitazone
While a causal relationship between dapagliflozin and bladder cancer is unlikely (see sections 4.8 and 5.3), as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.

Elevated haematocrit
Haematocrit increase was observed with dapagliflozin treatment (see section 4.8); therefore, caution in patients with already elevated haematocrit is warranted.

Combinations not studied
Dapagliflozin has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon-like peptide 1 (GLP-1) analogues.

Urine laboratory assessments
Due to its mechanism of action, patients taking Forxiga will test positive for glucose in their urine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Diuretics
Dapagliflozin may add to the diuretic effect of thiazide 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, 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 dapagliflozin (see sections 4.2 and 4.8).

Pharmacokinetic interactions
The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin
Interaction studies conducted in healthy subjects, using mainly a single dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products
In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant**.**

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

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 5.3). Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy.

When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Breast-feeding
It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring (see section 5.3). A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Fertility
The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

4.7 Effects on ability to drive and use machines

Forxiga has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile
In a pre-specified pooled analysis of 12 placebo-controlled studies, 1,193 subjects were treated with dapagliflozin 10 mg and 1,393 were treated with placebo.

The overall incidence of adverse events (short-term treatment) in subjects treated with dapagliflozin 10 mg was similar to placebo. Few adverse events led to discontinuation of treatment and were balanced across study groups. The most commonly reported events leading to discontinuation in patients treated with dapagliflozin 10 mg were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%). One subject receiving dapagliflozin experienced a liver adverse event with diagnoses of drug induced hepatitis and/or autoimmune hepatitis.

The most frequently reported adverse reaction was hypoglycaemia, which depended on the type of background therapy used in each study. The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add-on sulphonylurea (SU) and add-on insulin therapies. Combination therapies with sulphonylurea and add-on insulin had higher rates of hypoglycaemia (see *Hypoglycaemia* below).

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical trials. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse reactions in placebo-controlled studies[a]

System organ class	**Very common**	**Common***	**Uncommon****
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[b,c] Urinary tract infection[b]	Vulvovaginal pruritus
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst
Gastrointestinal disorders			Constipation
Skin and subcutaneous tissue disorders			Hyperhidrosis
Musculoskeletal and connective tissue disorders		Back pain	
Renal and urinary disorders		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]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.
[d]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.
[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.
[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 2.15% for dapagliflozin 10 mg versus -0.40% for placebo.
*Reported in ≥ 2% of subjects treated with dapagliflozin 10 mg and ≥ 1% more frequently than placebo.
**Reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg regardless of glycaemic rescue compared to placebo.

Description of selected adverse reactions

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in each study.

The frequency of minor episodes of hypoglycaemia was similar (< 4%) between treatment groups, including placebo. Across all studies, major events of hypoglycaemia were uncommon and

comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add on insulin therapies had higher rates of hypoglycaemia (see section 4.5).

In an add-on to glimepiride study, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0%) than in the placebo plus glimepiride group (2.1%).

In an add-on to insulin study, minor episodes were reported more frequently in the group treated with dapagliflozin 10 mg plus insulin (40.3%) than in the placebo plus insulin group (34.0%).

Volume depletion
Reactions related to volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 0.8% and 0.4% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo (see section 4.4).

Vulvovaginitis, balanitis and related genital infections
Vulvovaginitis, balanitis and related genital infections were reported in 4.8% and 0.9% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (9.7% and 3.4% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

Urinary tract infections
Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.3% versus 3.7%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

Parathyroid hormone (PTH)
Small increases in serum PTH levels were observed with increases being larger in subjects with higher baseline PTH concentrations. Bone mineral density measurements in patients with normal or mildly impaired renal function did not indicate bone loss over a treatment period of one year.

Malignancies
During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.

Special populations
Elderly patients (≥ 65 years)
In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 2.5% of subjects treated with dapagliflozin and 1.1% of subjects treated with placebo (see section 4.4). The most commonly reported adverse reaction related to renal function was increased serum creatinine. The majority of these reactions were transient and reversible. In subjects ≥ 65 years of age, adverse reactions of volume depletion, most commonly reported as hypotension, were reported in

1.5% and 0.4% of dapagliflozin-treated subjects and placebo-treated subjects, respectively (see section 4.4).

4.9 Overdose

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Other blood glucose lowering drugs, excluding insulins, ATC code: A10BX09

Mechanism of action
Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2).

The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 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, reabsorption of filtered glucose continues. Dapagliflozin improves 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 GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with Forxiga.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. 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 > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects
Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 ml/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/l (-0.87 to -0.33 mg/dl).

Clinical efficacy and safety
Eleven double-blind, randomised, controlled clinical trials were conducted with 5,693 subjects with type 2 diabetes to evaluate the efficacy and safety of Forxiga; 3,939 subjects in these studies were treated with dapagliflozin. Ten studies had a treatment period of 24 weeks duration, 5 with long-term extensions ranging from 24 to 78 weeks (up to a total study duration of 102 weeks), and one study was 52 weeks in duration. Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty-one percent had mild renal impairment and 12% had moderate renal impairment. Fifty-one percent (51%) of the subjects were men, 84% were White, 10% were Asian, 3% were Black and 3% were of other racial groups. Eighty percent (80%) of the subjects had a body mass index (BMI) ≥ 27.

Glycaemic control
Monotherapy
A double-blind, placebo-controlled study of 24-week duration (with an additional extension period) was conducted to evaluate the safety and efficacy of monotherapy with Forxiga in subjects with inadequately controlled type 2 diabetes mellitus. Once-daily treatment with dapagliflozin resulted in statistically significant ($p < 0.0001$) reductions in HbA1c compared to placebo (Table 2).

In the extension period, HbA1c reductions were sustained through Week 102 (-0.63%, and -0.18% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively).

Table 2. Results at Week 24 (LOCF[a]) of a placebo-controlled study of dapagliflozin as monotherapy

	Monotherapy	
	Dapagliflozin 10 mg	**Placebo**
N[b]	70	75
HbA1c (%)		
Baseline (mean)	8.01	7.79
Change from baseline[c]	-0.89	-0.23
Difference from placebo[c]	-0.66[*]	
(95% CI)	(-0.96, -0.36)	
Subjects (%) achieving: HbA1c < 7%		
Adjusted for baseline	50.8[§]	31.6
Body weight (kg)		
Baseline (mean)	94.13	88.77
Change from baseline[c]	-3.16	-2.19
Difference from placebo[c]	-0.97	
(95% CI)	(-2.20, 0.25)	

[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward
[b]All randomised subjects who took at least one dose of double-blind study medication during the short-term double-blind period
[c]Least squares mean adjusted for baseline value
[*]p-value < 0.0001 versus placebo
[§] Not evaluated for statistical significance as a result of the sequential testing procedure for secondary end points

Combination therapy
In a 52-week, active-controlled non-inferiority study, Forxiga was evaluated as add-on therapy to metformin compared with a sulphonylurea (glipizide) as add-on therapy to metformin in subjects with inadequate glycaemic control (HbA1c > 6.5% and ≤ 10%). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared to glipizide, thus demonstrating non-inferiority (Table 3). A significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%) experienced at least one event of hypoglycaemia over 52 weeks of treatment compared to the group treated with glipizide (40.8%).

Table 3. Results at Week 52 (LOCF[a]) in an active-controlled study comparing dapagliflozin to glipizide as add-on to metformin

Parameter	**Dapagliflozin + metformin**	**Glipizide + metformin**
N[b]	400	401
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline[c]	-0.52	-0.52
Difference from glipizide + metformin[c]	0.00[d]	
(95% CI)	(-0.11, 0.11)	
Body weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline[c]	-3.22	1.44
Difference from glipizide + metformin[c]	-4.65[*]	
(95% CI)	(-5.14, -4.17)	

[a]LOCF: Last observation carried forward
[b]Randomised and treated subjects with baseline and at least 1 post-baseline efficacy measurement
[c]Least squares mean adjusted for baseline value
[d]Non-inferior to glipizide + metformin
[*]p-value < 0.0001

Dapagliflozin as an add-on with either metformin, glimepiride or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p < 0.0001$; Tables 4 and 5).

Based on longitudinal repeated measures analysis, excluding data after rescue, the reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data. In addition, for the add-on to metformin study, HbA1c reductions were sustained through Week 102 (-0.78% and 0.02% adjusted mean change from baseline for 10 mg and placebo, respectively).

Table 4. Results of 24-week (LOCF[a]) placebo-controlled studies of dapagliflozin in add-on combination with metformin or glimepiride

	Add-on combination			
	Metformin[1]		**Sulphonylurea (glimepiride**[2]**)**	
	Dapagliflozin 10 mg	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**
N[b]	135	137	151	145
HbA1c (%)				
Baseline (mean)	7.92	8.11	8.07	8.15
Change from baseline[c]	-0.84	-0.30	-0.82	-0.13
Difference from placebo[c]	-0.54*		-0.68*	
(95% CI)	(-0.74, -0.34)		(-0.86, -0.51)	
Subjects (%) achieving: HbA1c < 7%				
Adjusted for baseline	40.6**	25.9	31.7*	13.0
Body weight (kg)				
Baseline (mean)	86.28	87.74	80.56	80.94
Change from baseline[c]	-2.86	-0.89	-2.26	-0.72
Difference from placebo[c]	-1.97*		-1.54*	
(95% CI)	(-2.63, -1.31)		(-2.17, -0.92)	

[1]Metformin ≥ 1500 mg/day; [2]glimepiride 4 mg/day

[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

[c]Least squares mean adjusted for baseline value

*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product

**p-value < 0.05 versus placebo + oral glucose-lowering medicinal product

Table 5. Results at Week 24 (LOCF[a]) in a placebo-controlled study of dapagliflozin in combination with insulin (alone or with oral glucose-lowering medicinal products)

Parameter	Dapagliflozin 10 mg + insulin ± oral glucose-lowering medicinal products[2]	Placebo + insulin ± oral glucose-lowering medicinal products[2]
N[b]	194	193
HbA1c (%)		
Baseline (mean)	8.58	8.46
Change from baseline[c]	-0.90	-0.30
Difference from placebo[c]	-0.60*	
(95% CI)	(-0.74, -0.45)	
Body weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline[c]	-1.67	0.02
Difference from placebo[c]	-1.68*	
(95% CI)	(-2.19, -1.18)	
Mean daily insulin dose (IU)[1]		
Baseline (mean)	77.96	73.96
Change from baseline[c]	-1.16	5.08
Difference from placebo[c]	-6.23*	
(95% CI)	(-8.84, -3.63)	
Subjects with mean daily insulin dose reduction of at least 10% (%)	19.6**	11.0

[a]LOCF: Last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

[c]Least squares mean adjusted for baseline value and presence of oral glucose-lowering medicinal product

*p-value < 0.0001 versus placebo + insulin ± oral glucose-lowering medicinal product

**p-value < 0.05 versus placebo + insulin ± oral glucose-lowering medicinal product

[1]Up-titration of insulin regimens (including short-acting, intermediate, and basal insulin) was only allowed if subjects met pre-defined FPG criteria.

[2]Fifty percent of subjects were on insulin monotherapy at baseline; 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group, 80% were on metformin alone, 12% were on metformin plus sulphonylurea therapy, and the rest were on other oral glucose-lowering medicinal products.

Fasting plasma glucose

Treatment with dapagliflozin 10 mg as a monotherapy or as an add-on to either metformin, glimepiride or insulin resulted in statistically significant reductions in fasting plasma glucose (-1.64 to -1.20 mmol/l [-29.6 to -21.7 mg/dl]) compared to placebo (-0.33 to 0.18 mmol/l [-6.0 to 3.3 mg/dl]). This effect was observed at Week 1 of treatment and maintained in studies extended through Week 102.

Post-prandial glucose

Treatment with dapagliflozin 10 mg as an add-on to glimepiride resulted in statistically significant reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Body weight

Dapagliflozin 10 mg as an add-on to metformin, glimepiride or insulin resulted in statistically significant body weight reduction at 24 weeks. In longer-term trials, when added to metformin, these effects were sustained at 52 weeks (-4.65 kg reduction versus glipizide) and 102 weeks (-3.07 kg reduction versus placebo).

A 24-week study in 182 diabetic subjects using dual energy X-ray absorptiometry (DXA) to evaluate body composition demonstrated reductions with dapagliflozin 10 mg plus metformin compared with placebo plus metformin, respectively, in body weight and body fat mass as measured by DXA rather than lean tissue or fluid loss. Treatment with Forxiga plus metformin showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment in a magnetic resonance imaging substudy.

Blood pressure
In a pre-specified pooled analysis of 12 placebo-controlled studies, treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of -4.4 mmHg and diastolic blood pressure of -2.1 mmHg versus -0.9 mmHg systolic and -0.5 mmHg diastolic blood pressure for placebo group at Week 24.

Cardiovascular safety
A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 36.6% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 70.0% had hypertension. Cardiovascular episodes were adjudicated by an independent adjudication committee. The primary end point was the time-to-first event of one of the following outcomes: cardiovascular death, stroke, myocardial infarction (MI) or hospitalisation for unstable angina. Primary episodes occurred at a rate of 1.64% per patient-year in subjects treated with dapagliflozin and 1.99% in comparator-treatment subjects, per patient-year. The hazard ratio comparing dapagliflozin to comparator was 0.82 (95% Confidence interval [CI]: 0.58, 1.15), indicating that in this analysis Forxiga is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI and stroke were observed with a hazard ratio of 0.79 (95% CI: 0.54, 1.17).

Patients with renal impairment
Moderate renal impairment (eGFR ≥ 30 to < 60 ml/min/1.73 m^2)
The efficacy of dapagliflozin was also assessed separately in a dedicated study of diabetic subjects with moderate renal impairment (252 subjects with mean eGFR 44 ml/min/1.73 m^2). The mean change from baseline in HbA1c at 24 weeks was -0.44% and -0.32%, for dapagliflozin 10 mg and placebo, respectively.

Patients with baseline HbA1c ≥ 9%
In a pre-specified analysis of subjects with baseline HbA1c ≥ 9.0%, treatment with dapagliflozin 10 mg resulted in statistically significant reductions in HbA1c at Week 24 as a monotherapy (adjusted mean change from baseline: -2.04% and 0.19% for dapagliflozin 10 mg and placebo, respectively) and as an add-on to metformin (adjusted mean change from baseline: -1.32% and -0.53% for dapagliflozin and placebo, respectively).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with dapagliflozin in one or more subsets of the paediatric population in the treatment of type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC_{τ} values following once daily 10 mg doses of dapagliflozin were 158 ng/ml and 628 ng h/ml, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. 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. Hence, Forxiga can be administered with or without food.

Distribution
Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 l.

Biotransformation
Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. 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
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. The mean total systemic clearance of dapagliflozin administered intravenously was 207 ml/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [^{14}C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Linearity
Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Special populations
Renal impairment
At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. 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 subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on dapagliflozin exposure is not known.

Hepatic impairment
In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), 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. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Elderly patients (≥ 65 years)
There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Paediatric population
Pharmacokinetics in the paediatric population have not been studied.

Gender
The mean dapagliflozin AUC_{ss} in females was estimated to be about 22% higher than in males.

Race
There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight
Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Reproductive and developmental toxicity
Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed *in utero* and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460i)
Lactose, anhydrous
Crospovidone (E1201)
Silicon dioxide (E551)
Magnesium stearate (E470b)

Film-coating
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/Alu blister
Pack sizes of 14, 28 and 98 film-coated tablets in non-perforated calendar blisters
Pack sizes of 30x1 and 90x1 film-coated tablets in perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
IT-03012 Anagni (FR)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 5 mg film-coated tablets
dapagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
90x1 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Forxiga 5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 10 mg film-coated tablets
dapagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dapagliflozin propanediol monohydrate equivalent to10 mg dapagliflozin

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
90x1 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Forxiga 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS PERFORATED UNIT DOSE 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 5 mg tablets
dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS PERFORATED UNIT DOSE 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 10 mg tablets
dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTERS NON-PERFORATED 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 5 mg tablets
dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTERS NON-PERFORATED 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 10 mg tablets
dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Forxiga 5 mg film-coated tablets
Forxiga 10 mg film-coated tablets
dapagliflozin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Forxiga is and what it is used for

Forxiga contains the active substance dapagliflozin. It belongs to a group of medicines called "oral anti-diabetics".
- These are medicines taken by mouth for diabetes.
- They work by lowering the amount of sugar (glucose) in your blood.

Forxiga is used for a type of diabetes called "type 2 diabetes mellitus" in adult patients (aged 18 years and older). "Type 2 diabetes mellitus" is the type of diabetes that usually starts when you are older. If you have type 2 diabetes, your pancreas does not make enough insulin or your body is not able to use the insulin it produces properly. This leads to a high level of sugar in your blood. Forxiga works by removing excess sugar from your body via your urine.
- Forxiga is used if your diabetes cannot be controlled with other medicines for diabetes, diet and exercise.
- Your doctor may ask you to take Forxiga on its own if you are intolerant to metformin or together with other medicines to treat diabetes. This may be another medicine taken by mouth and/or insulin given by injection.

It is important to continue to follow the advice on diet and exercise given to you by your doctor, pharmacist or nurse.

2. What you need to know before you take Forxiga

Do not take Forxiga:
- if you are allergic to dapagliflozin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Forxiga:
- if you have "type 1 diabetes" – the type that usually starts when you are young, and your body does not produce any insulin.
- if you have increased levels of "ketone bodies" in your urine or blood, seen in tests. This is a sign of "diabetic ketoacidosis" – a problem you can get with diabetes whose signs include rapid weight loss, feeling sick or being sick, a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat.
- if you have a kidney problem – your doctor may ask you to take a different medicine.
- if you have a liver problem – your doctor may start you on a lower dose.
- if you have a history of serious heart disease or if you have had a stroke.
- if you are are on medicines to lower your blood pressure (anti-hypertensives) and have a history of low blood pressure (hypotension). More information is given below in **Other medicines and Forxiga.**
- if you have very high levels of glucose in your blood which may make you dehydrated (lose too much body fluid). Possible signs of dehydration are listed at the top of section 4, 'Possible side effects'. Tell your doctor before you start taking Forxiga if you have any of these signs.
- if you have or develop nausea (feeling sick), vomiting or fever or if you are not able to eat or drink. These conditions can cause dehydration. Your doctor may ask you to stop taking Forxiga until you recover to prevent dehydration.
- if you often get infections of the urinary tract.
- if you are 75 years old or older, you should not start taking Forxiga.
- if you are taking another medicine for diabetes that contains "pioglitazone", you should not start taking Forxiga.
- if you have an increase in the amount of red blood cells in your blood, seen in tests.

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

Kidney function
Your kidneys should be checked before you start taking and whilst you are on this medicine.

Urine glucose
Because of how Forxiga works, your urine will test positive for sugar while you are on this medicine.

Children and adolescents
Forxiga is not recommended for children and adolescents under 18 years of age, because it has not been studied in these patients.

Other medicines and Forxiga
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
Especially tell your doctor:
- if you are taking a medicine used to remove water from the body (diuretic). Your doctor may ask you to stop taking Forxiga. Possible signs of losing too much fluid from your body are listed at the top of section 4 'Possible side effects'.
- if 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 the dose of these other medicines, to prevent you from getting low blood sugar levels (hypo-glycaemia).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should stop taking this medicine if you become pregnant, since it is not recommended during the second and third trimesters of pregnancy. Talk to your doctor about the best way to control your blood sugar while you are pregnant.

Talk to your doctor if you would like to or are breast-feeding before taking this medicine. Do not use Forxiga if you are breast-feeding. It is not known if this medicine passes into human breast milk.

Driving and using machines
Forxiga has no or negligible influence on the ability to drive and use machines. Taking this medicine with other medicines called sulphonylureas or with insulin can cause too low blood sugar levels (hypo-glycaemia), 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 taking Forxiga.

Forxiga contains lactose
Forxiga contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Forxiga

Always take this medicine exactly as your doctor has told you. Check with your doctor, phamacist or nurse if you are not sure.

How much to take
- The recommended dose is one 10 mg tablet each day.
- Your doctor may start you on a 5 mg dose if you have a liver problem.
- Your doctor will prescribe the strength that is right for you.

Taking this medicine
- Swallow the tablet whole with half a glass of 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 another medicine to lower the amount of sugar in your blood. This may be a medicine by mouth or insulin given by injection. Remember to take this other medicine your doctor has told you. This will help get the best results for your health.

Diet and exercise
To control your diabetes, you still need to keep 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 doctor, pharmacist or nurse. In particular, if you are following a diabetic weight control diet, continue to follow it while you are taking Forxiga.

If you take more Forxiga than you should
If you take more Forxiga tablets than you should, talk to a doctor or go to a hospital immediately. Take the medicine pack with you.

If you forget to take Forxiga
What to do if you forget to take a tablet depends on how long it is until your next dose.
- If it is 12 hours or more until your next dose, take a dose of Forxiga as soon as you remember. Then take your next dose at the usual time.
- If it is less than 12 hours until your next dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose of Forxiga to make up for a forgotten dose.

If you stop taking Forxiga
Do not stop taking Forxiga without talking to your doctor first. Your blood sugar may increase without this medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Forxiga and see a doctor as soon as possible if you notice any of the following serious side effects:

- loss of too much fluid from your body (dehydration), seen uncommonly.

These are signs of dehydration:
- very dry or sticky mouth, feeling very thirsty
- feeling very sleepy or tired
- passing little or no water (urine)
- fast heart beat.

- urinary tract infection, seen commonly.

These are signs of a severe infection of the urinary tract:
- fever and/or chills
- burning sensation when passing water (urinating)
- pain in your back or side.

Although uncommon, if you see blood in your urine, tell your doctor immediately.

Contact your doctor as soon as possible if you have any of the following side effects:
Very common (may affect more than 1 in 10 people)
- low blood sugar levels (hypo-glycaemia) - when taking this medicine with a sulphonylurea or insulin

These are the signs of low blood sugar:
- 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 levels and what to do if you get any of the signs above.

Other side effects when taking Forxiga:
Common (may affect up to 1 in 10 people)
- yeast infection (thrush) of your penis or vagina
- back pain
- passing more water (urine) than usual or needing to pass water more often
- changes in the amount of cholesterol or fats in your blood (shown in tests)
- changes in the amount of red blood cells in your blood (shown in tests)

Uncommon (may affect up to 1 in 100 people)
- unusual vaginal bleeding, discharge, itching or odour
- thirst
- constipation
- excess sweating
- awakening from sleep at night to pass urine
- changes in laboratory blood tests (for example creatinine or urea)

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Forxiga

- Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date, which is stated on the blister or carton after 'EXP'. The expiry date refers to the last day of that month.

- This medicine does not require any special storage conditions.

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Forxiga contains

- The active substance is dapagliflozin.

Each Forxiga 5 mg film-coated tablet (tablet) contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.
Each Forxiga 10 mg film-coated tablet (tablet) contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

- The other ingredients are:
  - tablet core: microcrystalline cellulose (E460i), anhydrous lactose (see section 2 'Forxiga contains lactose'), crospovidone (E1201), silicon dioxide (E551), magnesium stearate (E470b).
  - film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350, talc (E553b), yellow iron oxide (E172).

What Forxiga looks like and contents of the pack

- Forxiga 5 mg film-coated tablets are yellow and round with diameter of 0.7 cm. They have "5" on one side and "1427" on the other side.
- Forxiga 10 mg film-coated tablets are yellow and diamond-shaped approximately 1.1 x 0.8 cm diagonally. They have "10" on one side and "1428" on the other side.

Forxiga 5 mg tablets and Forxiga 10 mg tablets are available in aluminium blisters in pack sizes of 14, 28 or 98 film-coated tablets in non-perforated calendar blisters and 30x1 or 90x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed in your country.

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Manufacturer
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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu