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 5 mg 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

Type 2 diabetes mellitus
Forxiga is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Type 1 diabetes mellitus
Forxiga is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI $\geq$ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

4.2 Posology and method of administration

Posology
Type 2 diabetes mellitus
The recommended dose is 10 mg dapagliflozin once daily.

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).

Type 1 diabetes mellitus
Treatment with Forxiga is to be initiated and supervised by specialists in type 1 diabetes.

The recommended dose is 5 mg once daily.

Dapagliflozin must only be administered as an adjunct to insulin.

Before initiating treatment with dapagliflozin:

- Risk factors for diabetic ketoacidosis (DKA) should be assessed (see section 4.4).
- It should be ensured that ketone levels are normal. If ketones are elevated (blood beta-hydroxybutyrate reading greater than 0.6 mmol/L or urine ketones one plus (+)), treatment with dapagliflozin should not be started until the ketone levels are normal (see section 4.4).
- It should be ensured that the patient demonstrates the ability to monitor ketone levels.
- It is recommended that patients obtain several baseline ketone levels over one to two weeks prior to initiation of dapagliflozin therapy, and patients should become familiar with how their behaviours and circumstances affect their ketone levels.
- Patients should be informed, in a dedicated education session, on the risk of DKA, how to recognize DKA risk factors, signs or symptoms, how and when to monitor ketone levels and what actions to take at elevated ketone readings (see section 4.4).
- Correction of volume depletion prior to initiation of dapagliflozin is recommended in patients with this condition (see section 4.4).

In order to avoid hypoglycaemia with the first dose of dapagliflozin, a 20% reduction in the first mealtime bolus insulin may be considered. Subsequent bolus doses should be adjusted individually based on blood glucose results. No reduction in basal insulin is recommended when initiating dapagliflozin. Subsequently, basal insulin should be adjusted based on blood glucose results. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

Ketone monitoring during treatment:
During the initial one to two weeks of treatment with dapagliflozin, ketones should be monitored on a regular basis, then the frequency of ketone level testing should be individualized, according to the patient's lifestyle and/or risk factors (see section 4.4).

Patients should be informed about what actions to take if ketone levels are elevated. The recommended actions are listed in Table 1. Measurement of blood ketone levels is preferred to urine.

Table 1

Clinical stage	**Blood Ketone (beta-hydroxybutyrate)**	**Urine Ketone**	**Actions**
Ketonaemia	0.6-1.5 mmol/L	Trace or Small +	The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates if the glucose levels are normal or low. Ketone levels should be measured again after two hours. The patient should immediately seek medical advice and stop taking dapagliflozin if levels persist and symptoms present.
Impending DKA	> 1.5-3.0 mmol/L	Moderate ++	The patient should immediately seek medical advice and stop taking dapagliflozin. The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider

			taking extra carbohydrates if the glucose levels are normal or low. Ketone levels should be measured again after two hours.
Probable DKA	> 3.0 mmol/L	Large to very large +++ / ++++	The patient should go to emergency department without delay and stop taking dapagliflozin. The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates if the glucose levels are normal or low.

Special populations
Renal impairment
Forxiga should not be initiated in patients with a glomerular filtration rate [GFR] < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min (see sections 4.4, 4.8, 5.1 and 5.2).

No dose adjustment is required based on renal function.

Hepatic impairment
No dose 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 when indicated (see sections 4.1 of the 10 mg SmPC, 4.4 and 5.2).

Elderly (≥ 65 years)
In general, no dose 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).

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

Renal impairment
The glycaemic efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (GFR < 60 mL/min), 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 should not be initiated in patients with a GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. Forxiga has not been studied in severe renal impairment (GFR < 30 mL/min) 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 with GFR < 60 mL/min, at least 2 to 4 times per year.

Hepatic impairment
There is limited experience in clinical studies 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 and/or hypotension
Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), 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).

Diabetic ketoacidosis
Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of DKA. Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 1 diabetes patients, type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse.

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

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Type 2 diabetes mellitus
Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).

In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Type 1 diabetes mellitus
In type 1 diabetes mellitus studies with dapagliflozin, patients had a higher number of DKA events compared with the placebo group (see section 4.8).

Before initiating dapagliflozin
Before starting treatment, patients should be evaluated with respect to DKA risk.
Dapagliflozin should not be initiated when patients are at a higher risk of DKA, such as:

- Patients with low insulin needs.
- Patient not on optimal insulin dose or who have recent issues with noncompliance or recurrent errors with insulin dosing and who are unlikely to maintain adequate insulin dosing.
- Patients with increased insulin requirements due to acute medical illness or surgery.
- Patients who insist on maintaining caloric restriction, carbohydrate restriction or ketogenic diet or who chronically under-dose insulin (e.g. in order to remain in a lipolytic state).
- Patients with recent or recurrent history of DKA.
- Patients with elevated ketones levels (BHB reading is greater than 0.6 mmol/L or urine ketones one plus (+)). If ketones are elevated (blood beta-hydroxybutyrate reading 0.6 mmol/L or greater), treatment with dapagliflozin should not be started until the ketone levels are normal (see section 4.2).
- Patients unable or unwilling to monitor ketones.
- Patients with excessive alcohol consumption or who use illicit drugs.

Patients using an insulin infusion pump have a higher risk of DKA and should be experienced with pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur (issues with insertion site, clogged tubing, empty reservoir, etc.) and use of supplemental insulin injections with pen or syringe as needed in case of pump failure. Patients should consider monitoring ketones levels three to four hours after changing pump materials. Patients using a pump should also check their ketone levels with any suspected insulin interruption, regardless of blood glucose levels. Insulin injections should be given within 2 hours of an unexplained high blood glucose/ketone value and dapagliflozin treatment should be interrupted.

- The patients should be educated on the risk of DKA, emphasizing that DKA could occur even when blood glucose levels are below 14 mmol/L (250 mg/dL).
- The patient should be informed how to recognize the risk factors which can predispose to ketosis (including starvation ketosis) and DKA and how to recognize DKA signs or symptoms.
- Dapagliflozin should only be given to patients who are able to monitor ketone levels and are educated in when it is most appropriate to do so.
- Dapagliflozin should only be given to patients with access to ketone testing materials and immediate access to a clinician if blood or urine ketones are elevated.
- The patients should be educated on what actions to take when ketosis/DKA is suspected and when to discontinue dapagliflozin therapy (see section 4.2).
- DKA should be treated as per standard of care. Supplemental carbohydrate may be required in addition to hydration and additional rapid insulin (see Table 1 in section 4.2).

In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

During treatment with dapagliflozin:

- Insulin therapy should be continuously optimised.
- When needed to prevent hypoglycaemia, insulin dose reduction should be done cautiously to avoid ketosis and DKA (see section 4.2).
- In the event of a marked reduction of insulin need, discontinuation of dapagliflozin should be considered.

Ketone monitoring:
The patient should be advised to test their ketone level (urine or blood) if signs or symptoms of ketoacidosis occur. Measurement of blood ketone levels is preferred to urine. Ketones should be monitored on a regular basis during the initial one to two weeks, then the frequency of ketone level testing should be individualised, according to the patient's lifestyle and/or risk factors (see section 4.2). Ketone levels should be also checked in situations that may predispose to or increase risk of DKA.

Patients must be informed about what actions to take if ketone levels are elevated. The recommended actions are listed in Table 1 (see section 4.2).

Necrotising fasciitis of the perineum (Fournier's gangrene)
Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Forxiga should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections
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 (≥ 65 years)
Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

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).

Cardiac failure
There is no experience in clinical studies with dapagliflozin in NYHA class IV.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

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. Patients with rare hereditary problems of galactose intolerance, total 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 in patients with type 2 diabetes mellitus (see sections 4.2 and 4.8).

In patients with type 1 diabetes mellitus and a known risk of frequent or severe hypoglycaemia, it may be necessary to reduce the insulin dose at the time of initiating treatment with dapagliflozin to decrease the risk of hypoglycaemia. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA (see section 4.2).

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.

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

Paediatric population
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
Type 2 diabetes mellitus
In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In the dapagliflozin cardiovascular outcomes study (see section 5.1), 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Type 1 diabetes mellitus
In two placebo-controlled studies in subjects with type 1 diabetes mellitus, 548 subjects were treated with dapagliflozin 5 mg plus adjustable insulin and 532 were treated with placebo plus adjustable insulin.

The most frequently reported adverse reactions associated with dapagliflozin in patients with type 1 diabetes mellitus were genital infections, which were more frequent in females. Diabetic ketoacidosis was reported with common frequency. See "Description of selected adverse reactions" and section 4.4.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. 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), and not known (cannot be estimated from the available data).

Table 2. Adverse reactions in placebo-controlled clinical studies[a] and postmarketing experience

System organ class	Very common	Common[*]	Uncommon[**]	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] Urinary tract infection[*,b,d]	Fungal infection[**]		Necrotising fasciitis of the perineum (Fournier's gangrene)[b,i]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]	Diabetic ketoacidosis (when used in type 1 diabetes mellitus)[b,i,k]	Volume depletion[b,e] Thirst[**]	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,i,l]	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation[**] Dry mouth[**]		
Skin and subcutaneous tissue disorders		Rash[j]			Angioedema
Musculoskeletal and connective tissue disorders		Back pain[*]			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia[**]		
Reproductive system and breast disorders			Vulvovaginal pruritus[**] Pruritus genital[**]		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[h]	Blood creatinine increased during initial treatment[**,b] Blood urea increased[**] Weight decreased[**]		

[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]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

[f]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

[g]Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus –0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

[h]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.

[i]See section 4.4

[j]Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.

[k]Frequency of adverse reaction was identified from the full study population in 2 placebo-controlled studies in subjects with type 1 diabetes mellitus.

[l]Reported in the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

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

[**]Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Clinical studies in type 2 diabetes mellitus

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% 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 (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the dapagliflozin cardiovascular outcomes study, the number of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

In the dapagliflozin cardiovascular outcomes study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

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

For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. 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, at Weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively).

In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at Weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at Weeks 24 and 104. At Weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea.

In the dapagliflozin cardiovascular outcomes study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

Volume depletion
In the 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% 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).

In the dapagliflozin cardiovascular outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and ACE-I/ARB use. In patients with eGFR < 60 mL/min/1.73 m^2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

Diabetic ketoacidosis
In the dapagliflozin cardiovascular outcomes study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

Urinary tract infections
In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, 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.

In the dapagliflozin cardiovascular outcomes study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

Increased creatinine
Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This

grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73 m^2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73 m^2 (18.5% dapagliflozin 10 mg versus 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the dapagliflozin cardiovascular outcomes study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m^2), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

Clinical studies in type 1 diabetes mellitus
The safety profile of dapagliflozin in subjects with type 1 diabetes mellitus was similar to the known safety profile of dapagliflozin in subjects with type 2 diabetes mellitus, with the exception of a higher number of DKA events in dapagliflozin-treated subjects in the type 1 diabetes mellitus studies.

Diabetic ketoacidosis
In the two placebo-controlled clinical studies of dapagliflozin in type 1 diabetes mellitus, patients were advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥ 0.6 mmol/L. In the pooled 52-week data, events of DKA were reported in 22 (4.0%) patients in the dapagliflozin 5 mg group and 6 (1.1%) patients in the placebo group, with corresponding incidence rates per 100 patient years of 4.62 for dapagliflozin 5 mg and 1.27 for placebo. DKA events occurred evenly distributed over the clinical study period. Inadequate insulin doses (missed insulin dose or insulin pump failure) were the most common precipitating factors. 6 of 23 events of DKA in the dapagliflozin 5 mg group occurred in patients with blood glucose in the euglycaemic range (< 14 mmol/L or 250 mg/dL).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK01

Mechanism of action
Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of 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
Type 2 diabetes mellitus
Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

Fourteen double-blind, randomised, controlled clinical studies were conducted with 7,056 subjects with type 2 diabetes to evaluate the glycaemic efficacy and safety of Forxiga; 4,737 subjects in these

studies were treated with dapagliflozin. Twelve studies had a treatment period of 24 weeks duration, 8 with long-term extensions ranging from 24 to 80 weeks (up to a total study duration of 104 weeks), one study had a 28-week treatment period, and one study was 52 weeks in duration with long-term extensions of 52 and 104 weeks (total study duration of 208 weeks). Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty percent (50%) had mild renal impairment and 11% had moderate renal impairment. Fifty-one percent (51%) of the subjects were men, 84% were White, 8% were Asian, 4% were Black and 4% were of other racial groups. Eighty-one percent (81%) of the subjects had a body mass index (BMI) ≥ 27. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

A cardiovascular outcomes study (DECLARE) was conducted with dapagliflozin 10 mg compared with placebo in 17,160 patients with type 2 diabetes mellitus with or without established cardiovascular disease to evaluate the effect on cardiovascular and renal events.

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 3).

In the extension period, HbA1c reductions were sustained through Week 102 (-0.61%, and -0.17% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively).

Table 3. 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

Add-on combination therapy
In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), 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 4). At Week 104, adjusted mean change from

baseline in HbA1c was -0.32% for dapagliflozin and -0.14% for glipizide. At Week 208, adjusted mean change from baseline in HbA1c was -0.10% for dapagliflozin and 0.20% for glipizide. At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%, 4.3% and 5.0%, respectively) experienced at least one event of hypoglycaemia compared to the group treated with glipizide (40.8%, 47.0% and 50.0%, respectively). The proportion of subjects remaining in the study at Week 104 and Week 208 was 56.2% and 39.7% for the group treated with dapagliflozin and 50.0% and 34.6% for the group treated with glipizide.

Table 4. 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, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p < 0.0001$; Tables 5, 6 and 7).

The reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data (glimepiride) and up to 104-week data (insulin). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.30% and 0.38%, respectively. 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). At Week 104 for insulin (with or without additional oral glucose-lowering medicinal products), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively. At Weeks 48 and 104, the insulin dose remained stable compared to baseline in subjects treated with dapagliflozin 10 mg at an average dose of 76 IU/day. In the placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline (mean average dose of 84 and 92 IU/day) at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with dapagliflozin 10 mg and 54.8% for the placebo group.

Table 5. Results of 24-week (LOCF[a]) placebo-controlled studies of dapagliflozin in add-on combination with metformin or sitagliptin (with or without metformin)

	Add-on combination			
	Metformin[1]		DPP-4 Inhibitor (sitagliptin[2]) ± Metformin[1]	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N[b]	135	137	223	224
HbA1c (%)				
Baseline (mean)	7.92	8.11	7.90	7.97
Change from baseline[c]	-0.84	-0.30	-0.45	0.04
Difference from placebo[c] (95% CI)	-0.54* (-0.74, -0.34)		-0.48* (-0.62, -0.34)	
Subjects (%) achieving: HbA1c < 7% Adjusted for baseline	40.6**	25.9		
Body weight (kg)				
Baseline (mean)	86.28	87.74	91.02	89.23
Change from baseline[c]	-2.86	-0.89	-2.14	-0.26
Difference from placebo[c] (95% CI)	-1.97* (-2.63, -1.31)		-1.89* (-2.37, -1.40)	

[1]Metformin ≥ 1500 mg/day;

[2]sitagliptin 100 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 6. Results of 24-week placebo-controlled studies of dapagliflozin in add-on combination with sulphonylurea (glimepiride) or metformin and a sulphonylurea

	Add-on combination			
	Sulphonylurea (glimepiride[1])		Sulphonylurea + Metformin[2]	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N[a]	151	145	108	108
HbA1c (%)[b]				
Baseline (mean)	8.07	8.15	8.08	8.24
Change from baseline[c]	-0.82	-0.13	-0.86	-0.17
Difference from placebo[c]	-0.68*		−0.69*	
(95% CI)	(-0.86, -0.51)		(−0.89, −0.49)	
Subjects (%) achieving: HbA1c < 7% (LOCF)[d]				
Adjusted for baseline	31.7*	13.0	31.8*	11.1
Body weight (kg) (LOCF)[d]				
Baseline (mean)	80.56	80.94	88.57	90.07
Change from baseline[c]	-2.26	-0.72	-2.65	-0.58
Difference from placebo[c]	-1.54*		−2.07*	
(95% CI)	(-2.17, -0.92)		(−2.79, −1.35)	

[1]glimepiride 4 mg/day;

[2]Metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrolment.

[a]Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[b]Columns 1 and 2, HbA1c analysed using LOCF (see footnote d); Columns 3 and 4, HbA1c analysed using LRM (see footnote e)

[c]Least squares mean adjusted for baseline value

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

[e]LRM: Longitudinal repeated measures analysis

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

Table 7. 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% (%)	19.7[**]	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.

In combination with metformin in drug-naive patients
A total of 1,236 drug-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥ 7.5% and ≤ 12%) participated in two active-controlled studies of 24 weeks duration to evaluate the efficacy and safety of dapagliflozin (5 mg or 10 mg) in combination with metformin in drug-naive patients versus therapy with the monocomponents.

Treatment with dapagliflozin 10 mg in combination with metformin (up to 2000 mg per day) provided significant improvements in HbA1c compared to the individual components (Table 8), and led to greater reductions in fasting plasma glucose (FPG) (compared to the individual components) and body weight (compared to metformin).

Table 8. Results at Week 24 (LOCF[a]) in an active-controlled study of dapagliflozin and metformin combination therapy in drug-naive patients

Parameter	Dapagliflozin 10 mg + Metformin	Dapagliflozin 10 mg	Metformin
N[b]	211[b]	219[b]	208[b]
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline[c]	-1.98	-1.45	-1.44
Difference from dapagliflozin[c]	−0.53*		
(95% CI)	(−0.74, −0.32)		
Difference from metformin[c]	−0.54*	−0.01	
(95% CI)	(−0.75, −0.33)	(−0.22, 0.20)	

[a]LOCF: last observation (prior to rescue for rescued patients) carried forward.
[b]All randomised patients 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.

Combination therapy with prolonged-release exenatide
In a 28-week, double-blind, active comparator-controlled study, the combination of dapagliflozin and prolonged-release exenatide (a GLP-1 receptor agonist) was compared to dapagliflozin alone and prolonged-release exenatide alone in subjects with inadequate glycaemic control on metformin alone (HbA1c ≥ 8% and ≤ 12%). All treatment groups had a reduction in HbA1c compared to baseline. The combination treatment with dapagliflozin 10 mg and prolonged-release exenatide group showed superior reductions in HbA1c from baseline compared to dapagliflozin alone and prolonged-release exenatide alone (Table 9).

Table 9. Results of one 28-week study of dapagliflozin and prolonged-release exenatide versus dapagliflozin alone and prolonged-release exenatide alone, in combination with metformin (intent to treat patients)

Parameter	Dapagliflozin 10 mg QD + Prolonged-release exenatide 2 mg QW	Dapagliflozin 10 mg QD + Placebo QW	Prolonged-release exenatide 2 mg QW + Placebo QD
N	**228**	**230**	**227**
HbA1c (%)			
Baseline (mean)	9.29	9.25	9.26
Change from baseline[a]	-1.98	-1.39	-1.60
Mean difference in change from baseline between combination and single medicinal product (95% CI)		-0.59* (-0.84, -0.34)	-0.38** (-0.63, -0.13)
Subjects (%) achieving HbA1c < 7%	44.7	19.1	26.9
Body weight (kg)			
Baseline (mean)	92.13	90.87	89.12
Change from baseline[a]	-3.55	-2.22	-1.56
Mean difference in change from baseline between combination and single medicinal product (95% CI)		-1.33* (-2.12, -0.55)	-2.00* (-2.79, -1.20)

QD=once daily, QW=once weekly, N=number of patients, CI=confidence interval.

[a]Adjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values at Week 28 are modelled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (< 9.0% or ≥ 9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.

[*]$p < 0.001$, [**]$p < 0.01$.

P-values are all adjusted p-values for multiplicity.

Analyses exclude measurements post rescue therapy and post premature discontinuation of study medicinal product.

Fasting plasma glucose

Treatment with dapagliflozin 10 mg as a monotherapy or as an add-on to either metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in FPG (-1.90 to -1.20 mmol/L [-34.2 to -21.7 mg/dL]) compared to placebo (-0.33 to 0.21 mmol/L [-6.0 to 3.8 mg/dL]). This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in significantly greater reductions in FPG at Week 28: -3.66 mmol/L (-65.8 mg/dL), compared to -2.73 mmol/L (-49.2 mg/dL) for dapagliflozin alone ($p < 0.001$) and -2.54 mmol/L (-45.8 mg/dL) for exenatide alone ($p < 0.001$).

In a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2, treatment with dapagliflozin demonstrated reductions in FPG at Week 24: -1.19 mmol/L (-21.46 mg/dL) compared to -0.27 mmol/L (-4.87 mg/dL) for placebo (p=0.001).

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.

Treatment with dapagliflozin 10 mg as an add-on to sitagliptin (with or without metformin) resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in significantly greater reductions in 2-hour post-prandial glucose at Week 28 compared to either medicinal product alone.

Body weight

Dapagliflozin 10 mg as an add-on to metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant body weight reduction at 24 weeks ($p < 0.0001$, Tables 5 and 6). These effects were sustained in longer-term studies. At 48 weeks, the difference for dapagliflozin as add-on to sitagliptin (with or without metformin) compared with placebo was -2.22 kg. At 102 weeks, the difference for dapagliflozin as add-on to metformin compared with placebo, or as add-on to insulin compared with placebo was -2.14 and -2.88 kg, respectively.

As an add-on therapy to metformin in an active-controlled non-inferiority study, dapagliflozin resulted in a statistically significant body weight reduction compared with glipizide of -4.65 kg at 52 weeks ($p < 0.0001$, Table 4) that was sustained at 104 and 208 weeks (-5.06 kg and –4.38 kg, respectively).

The combination of dapagliflozin 10 mg and prolonged-release exenatide demonstrated significantly greater weight reductions compared to either medicinal product alone (Table 9).

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 13 placebo-controlled studies, treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and -0.5 mmHg diastolic blood pressure for placebo group at Week 24. Similar reductions were observed up to 104 weeks.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in a significantly greater reduction in systolic blood pressure at Week 28 (-4.3 mmHg) compared to dapagliflozin alone (-1.8 mmHg, $p < 0.05$) and prolonged-release exenatide alone (-1.2 mmHg, $p < 0.01$).

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with dapagliflozin 10 mg or placebo. At Week 12 for both studies, dapagliflozin 10 mg plus usual antidiabetic treatment provided improvement in HbA1c and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

In a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2, treatment with dapagliflozin demonstrated reductions in seated systolic blood pressure at Week 24: -4.8 mmHg compared to -1.7 mmHg for placebo ($p < 0.05$).

Glycaemic control in patients with moderate renal impairment CKD 3A (eGFR ≥ 45 to < 60 mL/min/1.73 m^2)
The efficacy of dapagliflozin was assessed in a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2 who had inadequate glycaemic control on usual care. Treatment with dapagliflozin resulted in reductions in HbA1c and body weight compared with placebo (Table 10).

Table 10. Results at Week 24 of a placebo-controlled study of dapagliflozin in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2

	Dapagliflozin[a] 10 mg	**Placebo[a]**
N[b]	**159**	**161**
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline[b]	-0.37	-0.03
Difference from placebo[b] (95% CI)	-0.34* (-0.53, -0.15)	
Body weight (kg)		
Baseline (mean)	92.51	88.30
Percent change from baseline[c]	-3.42	-2.02
Difference in percent change from placebo[c] (95% CI)	-1.43* (-2.15, -0.69)	

[a] Metformin or metformin hydrochloride were part of the usual care in 69.4% and 64.0% of the patients for the dapagliflozin and placebo groups, respectively.
[b] Least squares mean adjusted for baseline value
[c] Derived from least squares mean adjusted for baseline value
* $p<0.001$

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).

Cardiovascular and renal outcomes
Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomised, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional cardiovascular risk factors (age ≥ 55 years in men or ≥ 60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use) or established cardiovascular disease.

Of 17,160 randomised patients, 6,974 (40.6%) had established cardiovascular disease and 10,186 (59.4%) did not have established cardiovascular disease. 8,582 patients were randomised to dapagliflozin 10 mg and 8,578 to placebo, and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female. In total, 22.4% had had diabetes for ≤ 5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR < 60 mL/min/1.73 m^2, and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ratio [UACR] ≥ 30 to ≤ 300 mg/g or > 300 mg/g, respectively).

Most patients (98%) used one or more diabetic medications at baseline, including metformin (82%), insulin (41%) and sulfonylurea (43%).

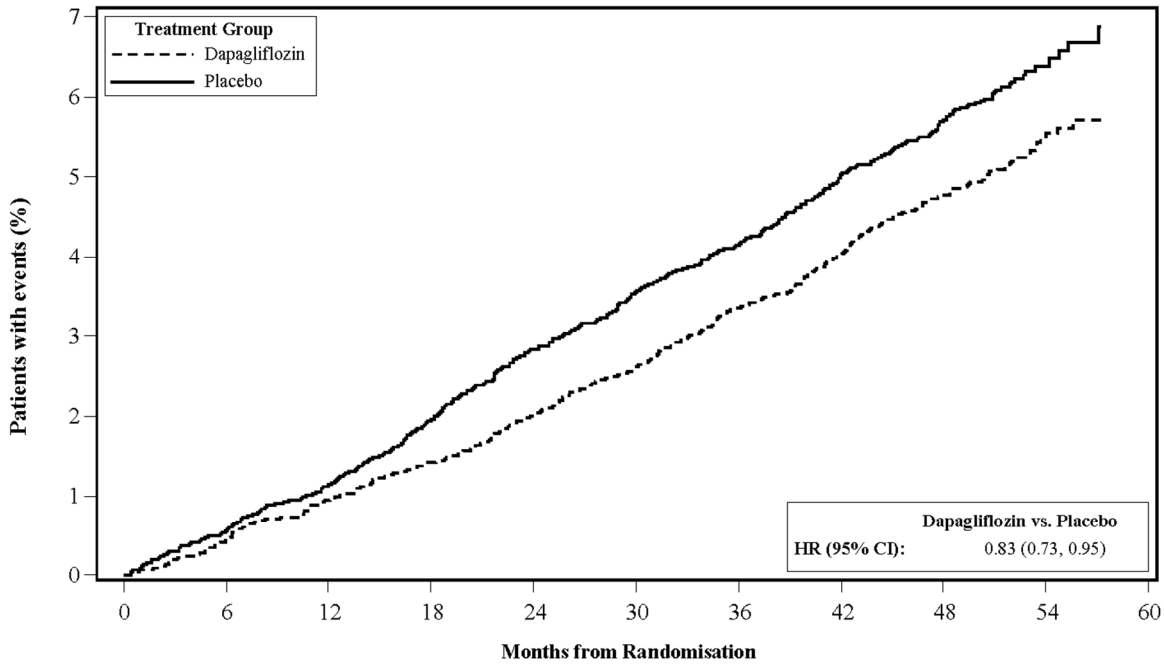
The primary endpoints were time to first event of the composite of cardiovascular death, myocardial infarction or ischaemic stroke (MACE) and time to first event of the composite of hospitalisation for heart failure or cardiovascular death. The secondary endpoints were a renal composite endpoint and all-cause mortality.

Major adverse cardiovascular events
Dapagliflozin 10 mg demonstrated non-inferiority versus placebo for the composite of cardiovascular death, myocardial infarction or ischaemic stroke (one-sided $p < 0.001$).

Heart failure or cardiovascular death
Dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalisation for heart failure or cardiovascular death (Figure 1). The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death (Figure 2).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established cardiovascular disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR) and region.

Figure 1: Time to first occurrence of hospitalisation for heart failure or cardiovascular death



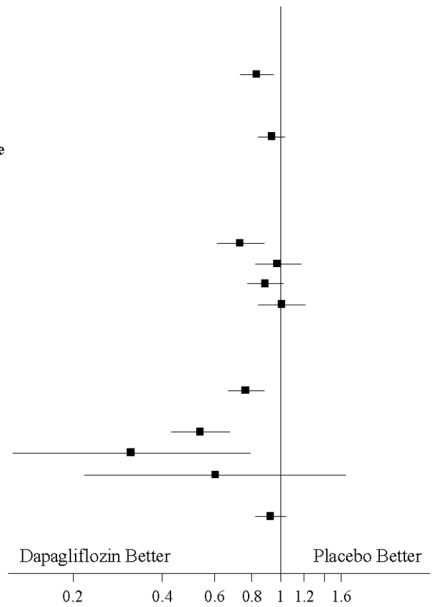
Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Patients at risk is the number of patients at risk at the beginning of the period.
HR=Hazard ratio CI=Confidence interval.

Results on primary and secondary endpoints are displayed in Figure 2. Superiority of dapagliflozin over placebo was not demonstrated for MACE (p=0.172). The renal composite endpoint and all-cause mortality were therefore not tested as part of the confirmatory testing procedure.

Figure 2: Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components



	Dapagliflozin n (%) (N=8582)	Placebo n (%) (N=8578)	Hazard Ratio (95% CI)	p-value
Primary endpoints				
Composite of hospitalisation for heart failure/cardiovascular death	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)	0.005
Composite of cardiovascular death/ myocardial infarction/ischaemic stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.172
Components of the composite endpoints				
Hospitalisation for heart failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)	<0.001
Cardiovascular death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
Myocardial infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.080
Ischaemic stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.916
Secondary endpoints				
Renal composite endpoint	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87)	<0.001
Renal components:				
Sustained eGFR decrease	120 (1.4)	221 (2.6)	0.54 (0.43, 0.67)	<0.001
End-stage renal disease	6 (<0.1)	19 (0.2)	0.31 (0.13, 0.79)	0.013
Renal death	6 (<0.1)	10 (0.1)	0.60 (0.22, 1.65)	0.324
All-cause mortality	529 (6.2)	570(6.6)	0.93 (0.82, 1.04)	0.198

Renal composite endpoint defined as: sustained confirmed ≥ 40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or end-stage renal disease (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m^2) and/or renal or cardiovascular death.

p-values are two-sided. p-values for the secondary endpoints and for single components are nominal. Time to first event was analysed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.
CI=confidence interval.

Nephropathy
Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, end-stage renal disease, renal or cardiovascular death. The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, end-stage renal disease and renal death (Figure 2).

The hazard ratio for time to nephropathy (sustained eGFR decrease, end-stage renal disease and renal death) was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

In addition, dapagliflozin reduced the new onset of sustained albuminuria (hazard ratio 0.79 [95% CI 0.72, 0.87]) and led to greater regression of macroalbuminuria (hazard ratio 1.82 [95% CI 1.51, 2.20]) compared with placebo.

Type 1 diabetes mellitus
Dapagliflozin as an adjunct to adjustable insulin was studied in two 24-week randomised, double-blind, placebo-controlled clinical studies with a 28-week extension to evaluate the efficacy and safety in adult patients with type 1 diabetes mellitus and inadequate glycaemic control (defined as HbA1c ≥ 7.5%) on insulin alone. Following an 8-week lead-in period to optimise each patient's diabetes management (glycaemic control including hyperglycaemia and hypoglycaemia, diet and exercise patterns), a total of 1,646 patients with HbA1c ≥ 7.5% and ≤ 10.5% were randomised to 5 mg dapagliflozin once daily, 10 mg dapagliflozin once daily or placebo once daily. Throughout the study, insulin dose was adjusted as deemed appropriate.

Glycaemic control
At Week 24, treatment with dapagliflozin once daily provided statistically significant improvements in HbA1c compared with placebo (Table 11). This finding was consistent across subgroups. At Week 52, adjusted mean changes from baseline in HbA1c relative to placebo were -0.33% and -0.20% for patients treated with dapagliflozin 5 mg, in the two studies, respectively. Treatment with dapagliflozin was not associated with an increase in percentage of patients with hypoglycaemic events compared with placebo. The number of patients with severe hypoglycaemia was balanced across treatment groups (6.9% and 7.5% at Week 24 in the dapagliflozin 5 mg and placebo groups, respectively).

The percentage of patients achieving ≥ 0.5% reductions in HbA1c without severe hypoglycaemia was significantly higher in patients treated with dapagliflozin compared with placebo (Table 11).

Table 11. Results at Week 24 of two placebo-controlled clinical studies of dapagliflozin as an adjunct to insulin in adults with type 1 diabetes mellitus

	Study MB102229		**Study MB102230**	
Efficacy Parameter	**Dapagliflozin 5 mg + Insulin**	**Placebo + Insulin**	**Dapagliflozin 5 mg + Insulin**	**Placebo + Insulin**
	N=259	**N=260**	**N=271**	**N=272**
HbA1c (%)				
Baseline (mean)	8.52	8.50	8.45	8.40
Change from baseline	-0.45	-0.03	-0.34	0.03
Difference from placebo	-0.42*		-0.37*	
95% CI	(-0.56, -0.28)		(-0.49, -0.26)	

	Study MB102229		Study MB102230	
Efficacy Parameter	**Dapagliflozin 5 mg + Insulin**	**Placebo + Insulin**	**Dapagliflozin 5 mg + Insulin**	**Placebo + Insulin**
Subjects (%) achieving ≥ 0.5% reductions in HbA1c without severe hypoglycaemia	49.6*	25.3	39.5*	20.1
Body weight (kg)				
Baseline (mean)	81.67	84.42	79.22	79.03
Change from baseline	-2.84	0.15	-2.50	0.06
Difference from placebo	-2.96*		-2.56*	
95% CI	(-3.63, -2.28)		(-3.12, -2.00)	

* $p < 0.0001$ versus placebo

Blood glucose variability
The adjusted mean changes for dapagliflozin 5 mg relative to placebo in the mean amplitude of glucose excursion from baseline to Week 24 were -0.96 mmol/L (-17.30 mg/dL) and -0.55 mmol/L (-9.85 mg/dL) in the two studies, respectively ($p < 0.0001$).

Statistically significant increases in the percentage of glucose readings falling within the range of > 70 mg/dL to ≤ 180 mg/dL from baseline to Week 24 for dapagliflozin 5 mg relative to placebo were +9.11% and +9.02% in the two studies, respectively ($p < 0.0001$). This increase was not accompanied by any increase in the percentage of 24-hour glucose readings < 70 mg/dL.

Insulin dose
Statistically significant ($p < 0.0001$) differences in percent reduction of total insulin dose from baseline for dapagliflozin 5 mg relative to placebo at Week 24 were -8.80% and -10.78% in the two studies, respectively.

Body weight
Statistically significant reductions in body weight were demonstrated for dapagliflozin compared with placebo (Table 11). Patients treated with dapagliflozin exhibited continuous weight loss over the 24-week period. At Week 52, the adjusted mean changes in body weight from baseline for dapagliflozin 5 mg relative to placebo were -2.56 kg and -3.50 kg, in the two studies, 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 mellitus and type 1 diabetes mellitus (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 liters.

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 faeces. In faeces, 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 haemodialysis 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 (≥ 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
Crospovidone (E1202)
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

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/795/001 14 film-coated tablets
EU/1/12/795/002 28 film-coated tablets
EU/1/12/795/003 98 film-coated tablets
EU/1/12/795/004 30 x 1 (unit dose) film-coated tablets
EU/1/12/795/005 90 x 1 (unit dose) film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2012
Date of latest renewal: 28 August 2017

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 10 mg 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 for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology
Type 2 diabetes mellitus
The recommended dose is 10 mg dapagliflozin once daily.

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
Forxiga should not be initiated in patients with a glomerular filtration rate [GFR] < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min (see sections 4.4, 4.8, 5.1 and 5.2).

No dose adjustment is required based on renal function.

Hepatic impairment
No dose 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 dose 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).

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

Renal impairment
The glycaemic efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (GFR < 60 mL/min), 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 should not be initiated in patients with a GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. Forxiga has not been studied in severe renal impairment (GFR < 30 mL/min) 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 with GFR < 60 mL/min, at least 2 to 4 times per year.

Hepatic impairment
There is limited experience in clinical studies 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 and/or hypotension
Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), 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).

Diabetic ketoacidosis
Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of diabetic ketoacidosis (DKA). Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 1 diabetes patients, type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse.

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

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Type 2 diabetes mellitus
Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).

In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Type 1 diabetes mellitus
In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin 10 mg should not be used for treatment of patients with type 1 diabetes.

Necrotising fasciitis of the perineum (Fournier's gangrene)
Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Forxiga should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections
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 (≥ 65 years)
Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

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).

Cardiac failure
There is no experience in clinical studies with dapagliflozin in NYHA class IV.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

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. Patients with rare hereditary problems of galactose intolerance, total 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 in patients with type 2 diabetes mellitus (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.

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

Paediatric population
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
Type 2 diabetes mellitus
In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In the dapagliflozin cardiovascular outcomes study (see section 5.1), 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. 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), and not known (cannot be estimated from the available data).

Table 1. Adverse reactions in placebo-controlled clinical studies[a] and postmarketing experience

System organ class	Very common	Common[*]	Uncommon[**]	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] Urinary tract infection[*,b,d]	Fungal infection[**]		Necrotising fasciitis of the perineum (Fournier's gangrene)[b,i]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst[**]	Diabetic ketoacidosis[b,i,k]	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation[**] Dry mouth[**]		
Skin and subcutaneous tissue disorders		Rash[j]			Angioedema
Musculoskeletal and connective tissue disorders		Back pain[*]			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia[**]		
Reproductive system and breast disorders			Vulvovaginal pruritus[**] Pruritus genital[**]		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[h]	Blood creatinine increased during initial treatment[**,b] Blood urea increased[**]		

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
			Weight decreased**		

[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]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.
[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.
[f]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.
[g]Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus –0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.
[h]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.
[i]See section 4.4
[j]Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.
[k]Reported in the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.
*Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.
**Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Clinical studies in type 2 diabetes mellitus

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% 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 (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the dapagliflozin cardiovascular outcomes study, the number of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

In the dapagliflozin cardiovascular outcomes study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

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

For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. 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, at Weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively).

In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at Weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at Weeks 24 and 104. At Weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea.

In the dapagliflozin cardiovascular outcomes study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

Volume depletion
In the 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% 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).

In the dapagliflozin cardiovascular outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and ACE-I/ARB use. In patients with eGFR < 60 mL/min/1.73 m^2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

Diabetic ketoacidosis
In the dapagliflozin cardiovascular outcomes study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

Urinary tract infections
In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, 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.

In the dapagliflozin cardiovascular outcomes study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

Increased creatinine
Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73 m^2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73 m^2 (18.5% dapagliflozin 10 mg versus 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the dapagliflozin cardiovascular outcomes study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m^2), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK01

Mechanism of action
Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of 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

Type 2 diabetes mellitus

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

Fourteen double-blind, randomised, controlled clinical studies were conducted with 7,056 subjects with type 2 diabetes to evaluate the glycaemic efficacy and safety of Forxiga; 4,737 subjects in these studies were treated with dapagliflozin. Twelve studies had a treatment period of 24 weeks duration, 8 with long-term extensions ranging from 24 to 80 weeks (up to a total study duration of 104 weeks), one study had a 28-week treatment period, and one study was 52 weeks in duration with long-term extensions of 52 and 104 weeks (total study duration of 208 weeks). Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty percent (50%) had mild renal impairment and 11% had moderate renal impairment. Fifty-one percent (51%) of the subjects were men, 84% were White, 8% were Asian, 4% were Black and 4% were of other racial groups. Eighty-one percent (81%) of the subjects had a body mass index (BMI) ≥ 27. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

A cardiovascular outcomes study (DECLARE) was conducted with dapagliflozin 10 mg compared with placebo in 17,160 patients with type 2 diabetes mellitus with or without established cardiovascular disease to evaluate the effect on cardiovascular and renal events.

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 (-0.61%, and -0.17% 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

Add-on combination therapy
In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), 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). At Week 104, adjusted mean change from baseline in HbA1c was -0.32% for dapagliflozin and -0.14% for glipizide. At Week 208, adjusted mean change from baseline in HbA1c was -0.10% for dapagliflozin and 0.20% for glipizide. At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%, 4.3% and 5.0%, respectively) experienced at least one event of hypoglycaemia compared to the group treated with glipizide (40.8%, 47.0% and 50.0%, respectively). The proportion of subjects remaining in the study at Week 104 and Week 208 was 56.2% and 39.7% for the group treated with dapagliflozin and 50.0% and 34.6% for the group treated with glipizide.

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, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p < 0.0001$; Tables 4, 5 and 6).

The reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data (glimepiride) and up to 104-week data (insulin). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.30% and 0.38%, respectively. 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). At Week 104 for insulin (with or without additional oral glucose-lowering medicinal products), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively. At Weeks 48 and 104, the insulin dose remained stable compared to baseline in subjects treated with dapagliflozin 10 mg at an average dose of 76 IU/day. In the placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline (mean average dose of 84 and 92 IU/day) at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with dapagliflozin 10 mg and 54.8% for the placebo group.

Table 4. Results of 24-week (LOCF[a]) placebo-controlled studies of dapagliflozin in add-on combination with metformin or sitagliptin (with or without metformin)

	Add-on combination			
	Metformin[1]		DPP-4 Inhibitor (sitagliptin[2]) ± Metformin[1]	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N[b]	135	137	223	224
HbA1c (%)				
Baseline (mean)	7.92	8.11	7.90	7.97
Change from baseline[c]	-0.84	-0.30	-0.45	0.04
Difference from placebo[c] (95% CI)	-0.54* (-0.74, -0.34)		-0.48* (-0.62, -0.34)	
Subjects (%) achieving: HbA1c < 7% Adjusted for baseline	40.6**	25.9		
Body weight (kg)				
Baseline (mean)	86.28	87.74	91.02	89.23
Change from baseline[c]	-2.86	-0.89	-2.14	-0.26
Difference from placebo[c] (95% CI)	-1.97* (-2.63, -1.31)		-1.89* (-2.37, -1.40)	

[1]Metformin ≥ 1500 mg/day;

[2]sitagliptin 100 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 of 24-week placebo-controlled studies of dapagliflozin in add-on combination with sulphonylurea (glimepiride) or metformin and a sulphonylurea

	Add-on combination			
	Sulphonylurea (glimepiride[1])		Sulphonylurea + Metformin[2]	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N[a]	151	145	108	108
HbA1c (%)[b]				
Baseline (mean)	8.07	8.15	8.08	8.24
Change from baseline[c]	-0.82	-0.13	-0.86	-0.17
Difference from placebo[c]	-0.68*		−0.69*	
(95% CI)	(-0.86, -0.51)		(−0.89, −0.49)	
Subjects (%) achieving: HbA1c < 7% (LOCF)[d]				
Adjusted for baseline	31.7*	13.0	31.8*	11.1
Body weight (kg) (LOCF)[d]				
Baseline (mean)	80.56	80.94	88.57	90.07
Change from baseline[c]	-2.26	-0.72	-2.65	-0.58
Difference from placebo[c]	-1.54*		−2.07*	
(95% CI)	(-2.17, -0.92)		(−2.79, −1.35)	

[1]glimepiride 4 mg/day;

[2]Metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrolment.

[a]Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[b]Columns 1 and 2, HbA1c analysed using LOCF (see footnote d); Columns 3 and 4, HbA1c analysed using LRM (see footnote e)

[c]Least squares mean adjusted for baseline value

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

[e]LRM: Longitudinal repeated measures analysis

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

Table 6. 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% (%)	19.7[**]	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.

In combination with metformin in drug-naive patients
A total of 1,236 drug-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥ 7.5% and ≤ 12%) participated in two active-controlled studies of 24 weeks duration to evaluate the efficacy and safety of dapagliflozin (5 mg or 10 mg) in combination with metformin in drug-naive patients versus therapy with the monocomponents.

Treatment with dapagliflozin 10 mg in combination with metformin (up to 2000 mg per day) provided significant improvements in HbA1c compared to the individual components (Table 7), and led to greater reductions in fasting plasma glucose (FPG) (compared to the individual components) and body weight (compared to metformin).

Table 7. Results at Week 24 (LOCF[a]) in an active-controlled study of dapagliflozin and metformin combination therapy in drug-naive patients

Parameter	Dapagliflozin 10 mg + Metformin	Dapagliflozin 10 mg	Metformin
N[b]	211[b]	219[b]	208[b]
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline[c]	-1.98	-1.45	-1.44
Difference from dapagliflozin[c]	−0.53*		
(95% CI)	(−0.74, −0.32)		
Difference from metformin[c]	−0.54*	−0.01	
(95% CI)	(−0.75, −0.33)	(−0.22, 0.20)	

[a]LOCF: last observation (prior to rescue for rescued patients) carried forward.
[b]All randomised patients 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.

Combination therapy with prolonged-release exenatide
In a 28-week, double-blind, active comparator-controlled study, the combination of dapagliflozin and prolonged-release exenatide (a GLP-1 receptor agonist) was compared to dapagliflozin alone and prolonged-release exenatide alone in subjects with inadequate glycaemic control on metformin alone (HbA1c ≥ 8% and ≤ 12%). All treatment groups had a reduction in HbA1c compared to baseline. The combination treatment with dapagliflozin 10 mg and prolonged-release exenatide group showed superior reductions in HbA1c from baseline compared to dapagliflozin alone and prolonged-release exenatide alone (Table 8).

Table 8. Results of one 28-week study of dapagliflozin and prolonged-release exenatide versus dapagliflozin alone and prolonged-release exenatide alone, in combination with metformin (intent to treat patients)

Parameter	Dapagliflozin 10 mg QD + Prolonged-release exenatide 2 mg QW	Dapagliflozin 10 mg QD + Placebo QW	Prolonged-release exenatide 2 mg QW + Placebo QD
N	**228**	**230**	**227**
HbA1c (%)			
Baseline (mean)	9.29	9.25	9.26
Change from baseline[a]	-1.98	-1.39	-1.60
Mean difference in change from baseline between combination and single medicinal product (95% CI)		-0.59* (-0.84, -0.34)	-0.38** (-0.63, -0.13)
Subjects (%) achieving HbA1c < 7%	44.7	19.1	26.9
Body weight (kg)			
Baseline (mean)	92.13	90.87	89.12
Change from baseline[a]	-3.55	-2.22	-1.56
Mean difference in change from baseline between combination and single medicinal product (95% CI)		-1.33* (-2.12, -0.55)	-2.00* (-2.79, -1.20)

QD=once daily, QW=once weekly, N=number of patients, CI=confidence interval.

[a]Adjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values at Week 28 are modelled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (< 9.0% or ≥ 9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.
[*]$p < 0.001$, [**]$p < 0.01$.
P-values are all adjusted p-values for multiplicity.
Analyses exclude measurements post rescue therapy and post premature discontinuation of study medicinal product.

Fasting plasma glucose
Treatment with dapagliflozin 10 mg as a monotherapy or as an add-on to either metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in FPG (-1.90 to -1.20 mmol/L [-34.2 to -21.7 mg/dL]) compared to placebo (-0.33 to 0.21 mmol/L [-6.0 to 3.8 mg/dL]). This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in significantly greater reductions in FPG at Week 28: -3.66 mmol/L (-65.8 mg/dL), compared to -2.73 mmol/L (-49.2 mg/dL) for dapagliflozin alone ($p < 0.001$) and -2.54 mmol/L (-45.8 mg/dL) for exenatide alone ($p < 0.001$).

In a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2, treatment with dapagliflozin demonstrated reductions in FPG at Week 24: -1.19 mmol/L (-21.46 mg/dL) compared to -0.27 mmol/L (-4.87 mg/dL) for placebo (p=0.001).

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.

Treatment with dapagliflozin 10 mg as an add-on to sitagliptin (with or without metformin) resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in significantly greater reductions in 2-hour post-prandial glucose at Week 28 compared to either medicinal product alone.

Body weight
Dapagliflozin 10 mg as an add-on to metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant body weight reduction at 24 weeks ($p < 0.0001$, Tables 4 and 5). These effects were sustained in longer-term studies. At 48 weeks, the difference for dapagliflozin as add-on to sitagliptin (with or without metformin) compared with placebo was -2.22 kg. At 102 weeks, the difference for dapagliflozin as add-on to metformin compared with placebo, or as add-on to insulin compared with placebo was -2.14 and -2.88 kg, respectively.

As an add-on therapy to metformin in an active-controlled non-inferiority study, dapagliflozin resulted in a statistically significant body weight reduction compared with glipizide of -4.65 kg at 52 weeks ($p < 0.0001$, Table 3) that was sustained at 104 and 208 weeks (-5.06 kg and –4.38 kg, respectively).

The combination of dapagliflozin 10 mg and prolonged-release exenatide demonstrated significantly greater weight reductions compared to either medicinal product alone (Table 8).

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 13 placebo-controlled studies, treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and -0.5 mmHg diastolic blood pressure for placebo group at Week 24. Similar reductions were observed up to 104 weeks.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in a significantly greater reduction in systolic blood pressure at Week 28 (-4.3 mmHg) compared to dapagliflozin alone (-1.8 mmHg, $p < 0.05$) and prolonged-release exenatide alone (-1.2 mmHg, $p < 0.01$).

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with dapagliflozin 10 mg or placebo. At Week 12 for both studies, dapagliflozin 10 mg plus usual antidiabetic treatment provided improvement in HbA1c and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

In a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2, treatment with dapagliflozin demonstrated reductions in seated systolic blood pressure at Week 24: -4.8 mmHg compared to -1.7 mmHg for placebo ($p < 0.05$).

Glycaemic control in patients with moderate renal impairment CKD 3A (eGFR ≥ 45 to < 60 mL/min/1.73 m^2)
The efficacy of dapagliflozin was assessed in a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2 who had inadequate glycaemic control on usual care. Treatment with dapagliflozin resulted in reductions in HbA1c and body weight compared with placebo (Table 9).

Table 9. Results at Week 24 of a placebo-controlled study of dapagliflozin in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2

	Dapagliflozin[a] 10 mg	**Placebo[a]**
N[b]	**159**	**161**
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline[b]	-0.37	-0.03
Difference from placebo[b] (95% CI)	-0.34* (-0.53, -0.15)	
Body weight (kg)		
Baseline (mean)	92.51	88.30
Percent change from baseline[c]	-3.42	-2.02
Difference in percent change from placebo[c] (95% CI)	-1.43* (-2.15, -0.69)	

[a] Metformin or metformin hydrochloride were part of the usual care in 69.4% and 64.0% of the patients for the dapagliflozin and placebo groups, respectively.
[b] Least squares mean adjusted for baseline value
[c] Derived from least squares mean adjusted for baseline value
* $p<0.001$

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).

Cardiovascular and renal outcomes
Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomised, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional cardiovascular risk factors (age ≥ 55 years in men or ≥ 60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use) or established cardiovascular disease.

Of 17,160 randomised patients, 6,974 (40.6%) had established cardiovascular disease and 10,186 (59.4%) did not have established cardiovascular disease. 8,582 patients were randomised to dapagliflozin 10 mg and 8,578 to placebo, and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female. In total, 22.4% had had diabetes for ≤ 5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR < 60 mL/min/1.73 m^2, and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ratio [UACR] ≥ 30 to ≤ 300 mg/g or > 300 mg/g, respectively).

Most patients (98%) used one or more diabetic medications at baseline, including metformin (82%), insulin (41%) and sulfonylurea (43%).

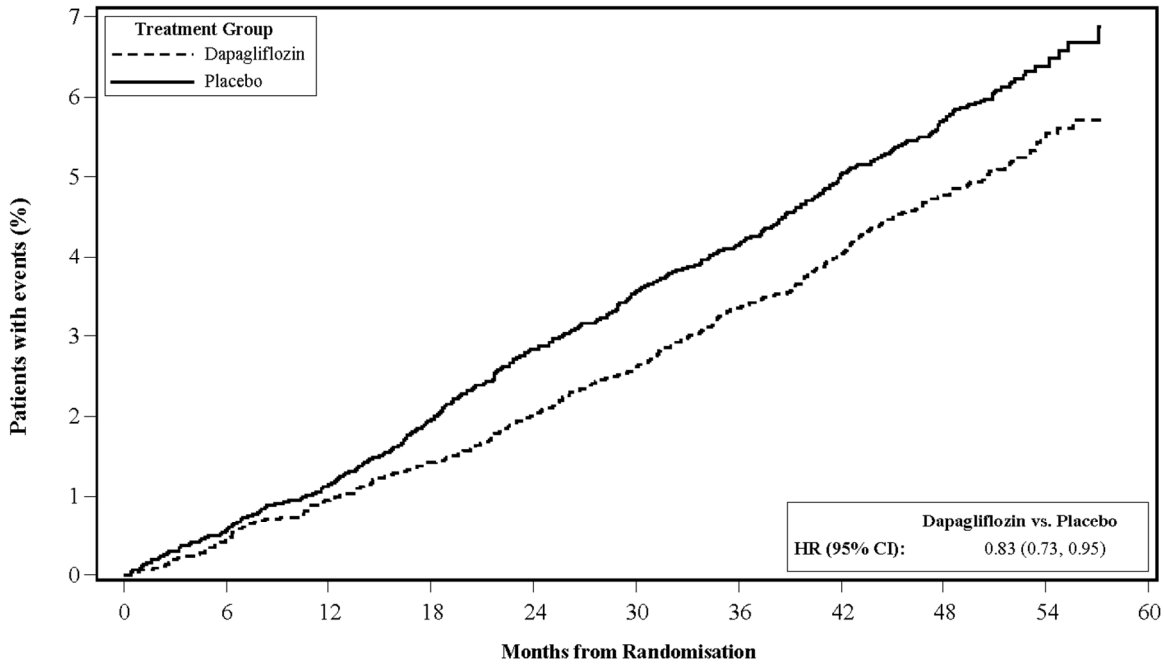
The primary endpoints were time to first event of the composite of cardiovascular death, myocardial infarction or ischaemic stroke (MACE) and time to first event of the composite of hospitalisation for heart failure or cardiovascular death. The secondary endpoints were a renal composite endpoint and all-cause mortality.

Major adverse cardiovascular events
Dapagliflozin 10 mg demonstrated non-inferiority versus placebo for the composite of cardiovascular death, myocardial infarction or ischaemic stroke (one-sided $p < 0.001$).

Heart failure or cardiovascular death
Dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalisation for heart failure or cardiovascular death (Figure 1). The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death (Figure 2).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established cardiovascular disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR) and region.

Figure 1: Time to first occurrence of hospitalisation for heart failure or cardiovascular death



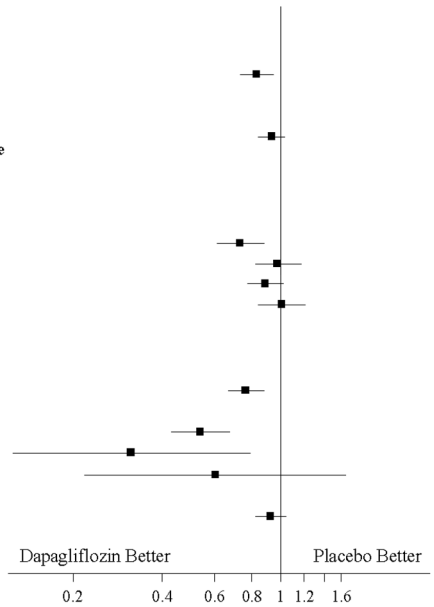
Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Patients at risk is the number of patients at risk at the beginning of the period.
HR=Hazard ratio CI=Confidence interval.

Results on primary and secondary endpoints are displayed in Figure 2. Superiority of dapagliflozin over placebo was not demonstrated for MACE (p=0.172). The renal composite endpoint and all-cause mortality were therefore not tested as part of the confirmatory testing procedure.

Figure 2: Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components



	Dapagliflozin n (%) (N=8582)	Placebo n (%) (N=8578)	Hazard Ratio (95% CI)	p-value
Primary endpoints				
Composite of hospitalisation for heart failure/cardiovascular death	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)	0.005
Composite of cardiovascular death/ myocardial infarction/ischaemic stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.172
Components of the composite endpoints				
Hospitalisation for heart failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)	<0.001
Cardiovascular death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
Myocardial infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.080
Ischaemic stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.916
Secondary endpoints				
Renal composite endpoint	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87)	<0.001
Renal components:				
Sustained eGFR decrease	120 (1.4)	221 (2.6)	0.54 (0.43, 0.67)	<0.001
End-stage renal disease	6 (<0.1)	19 (0.2)	0.31 (0.13, 0.79)	0.013
Renal death	6 (<0.1)	10 (0.1)	0.60 (0.22, 1.65)	0.324
All-cause mortality	529 (6.2)	570(6.6)	0.93 (0.82, 1.04)	0.198

Renal composite endpoint defined as: sustained confirmed ≥ 40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or end-stage renal disease (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m^2) and/or renal or cardiovascular death.

p-values are two-sided. p-values for the secondary endpoints and for single components are nominal. Time to first event was analysed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.
CI=confidence interval.

Nephropathy
Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, end-stage renal disease, renal or cardiovascular death. The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, end-stage renal disease and renal death (Figure 2).

The hazard ratio for time to nephropathy (sustained eGFR decrease, end-stage renal disease and renal death) was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

In addition, dapagliflozin reduced the new onset of sustained albuminuria (hazard ratio 0.79 [95% CI 0.72, 0.87]) and led to greater regression of macroalbuminuria (hazard ratio 1.82 [95% CI 1.51, 2.20]) compared with placebo.

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 liters.

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 faeces. In faeces, 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 haemodialysis 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 (≥ 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
Crospovidone (E1202)
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

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/795/006 14 film-coated tablets
EU/1/12/795/007 28 film-coated tablets
EU/1/12/795/008 98 film-coated tablets
EU/1/12/795/009 30 x 1 (unit dose) film-coated tablets
EU/1/12/795/010 90 x 1 (unit dose) film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2012
Date of latest renewal: 28 August 2017

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(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca GmbH
Tinsdaler Weg 183
22880 Wedel
Germany

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
SK10 2NA
United Kingdom

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Forxiga 5 mg Tablets
Type 1 diabetes: Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).
Type 2 diabetes: Medicinal product subject to medical prescription.

Forxiga 10 mg Tablets
Type 2 diabetes: Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures
Prior to launch of the new adult indication for dapagliflozin, for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy, in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials are aimed at providing guidance on how to manage risk of diabetic ketoacidosis (DKA) in patients with type 1 diabetes.

The MAH shall ensure that in each Member State where dapagliflozin is marketed for type 1 diabetes, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use the product have access to:
- Guide for Health Care Professionals including a prescriber's checklist
- Patient's/Carer's Guide
- Patient Alert Card

The guide for healthcare professionals including the prescriber's checklist should contain the following key elements:
- Dapagliflozin is not a substitute for insulin (and does not alter insulin-sensitivity).
- The risk of DKA is increased with dapagliflozin treatment.
- If treated with dapagliflozin, glucose levels will not adequately reflect insulin needs, and DKA may occur in patients treated with dapagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl). Therefore, glucose monitoring must be supplemented by ketone monitoring.
- Patients with euglycaemic DKA may need glucose in addition to standard of care treatment for DKA and dapagliflozin should be discontinued if DKA occurs.
- Guidance to the physician for assessing whether the patient is eligible for dapagliflozin prescription, e.g. patient selection criteria including adherence to insulin treatment and insulin thresholds, patient's beta-hydroxybutyrate (BHB) < 0.6 mmol/L or urine ketones < 1+, BMI ≥ 27 kg/m^2, absence of DKA risk factors.
- Guidance to the physician for assessing whether the patient is prepared and engaged to perform self-ketone testing before and during therapy.
- Summary of the recommendations for patients, particularly regarding blood ketone measurement and managing sick days.
- For pump users: restrict dapagliflozin prescription to patients experienced in pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur in case of pump failure.
- Counsel the patient and evaluate their adherence to ketone monitoring while establishing their baseline ketone level 1 to 2 weeks before treatment initiation and ensure the patient:
    - Has received education/training in ketone testing, and interpreting/acting upon test results
    - Is willing/able to perform ketone testing as prescribed
    - Is adequately informed about managing sick days
- Ensure the patient is on optimal insulin therapy prior to initiation of dapagliflozin treatment.
- Dapagliflozin treatment should be temporarily stopped before surgical procedures or in case of hospitalisation for acute serious illness.
- If addition of dapagliflozin leads to marked reduction of insulin need, discontinuation of dapagliflozin should be considered to avoid high risk of DKA.

The patient's/carer's guide should contain the following key elements:
- Dapagliflozin is not a substitute for insulin

- DKA may occur in patients treated with dapagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl), i.e. an explanation of the concept of euglycaemic DKA
- Signs/symptoms of DKA - if not adequately managed DKA can be severe and fatal.
- How to measure ketones, how to interpret the results and what to do in case of hyperketonaemia/DKA (contact HCP immediately if BHB > 0.6 mmol/L with symptoms or if BHB > 1.5 mmol/L with or without symptoms)
- Insulin dose reduction during treatment should only be done when needed to prevent hypoglycaemia and should be done cautiously to avoid ketosis and DKA
- Do not start caloric restriction or carbohydrate restriction while treated

The patient alert card should contain the following key elements:
- The Patient Alert Card should be presented to any HCP consulted.
- DKA may occur in patients treated with dapagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl).
- Signs/symptoms of DKA.
- Patients with euglycaemic DKA should receive glucose, insulin and fluids for DKA, dapagliflozin should be discontinued.
- Dapagliflozin should be temporarily stopped before surgical procedures or hospitalisation for acute serious illness.
- Contact details of the dapagliflozin prescriber' and 'Name of patient'.

Obligation to conduct post-authorisation measures:
The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional PASS: In order to estimate the incidence of DKA in T1DM dapagliflozin users following implementation of RMMs in Europe, the MAH should conduct and submit the results from an observational cohort study using existing data sources in European countries where dapagliflozin will be launched for T1DM.	31/12/2026

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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/795/001 14 film-coated tablets
EU/1/12/795/002 28 film-coated tablets
EU/1/12/795/003 98 film-coated tablets
EU/1/12/795/004 30 x 1 (unit dose) film-coated tablets
EU/1/12/795/005 90 x 1 (unit dose) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

forxiga 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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 to 10 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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/795/006 14 film-coated tablets
EU/1/12/795/007 28 film-coated tablets
EU/1/12/795/008 98 film-coated tablets
EU/1/12/795/009 30 x 1 (unit dose) film-coated tablets
EU/1/12/795/010 90 x 1 (unit dose) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

forxiga 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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

AstraZeneca AB

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

AstraZeneca AB

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

AstraZeneca AB

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

AstraZeneca AB

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
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. See section 4.

What is in this leaflet:

1. What Forxiga is and what it is used for

What Forxiga is
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 in adult patients (aged 18 years and older).

What Forxiga is used for
Forxiga is used for the types of diabetes called:
- type 1 diabetes – where your body hardly produces any insulin. Forxiga should only be used in type 1 diabetes patients who are overweight or obese.
- type 2 diabetes – where your body does not make enough insulin or is not able to use the insulin it produces properly.

In both types of diabetes, this leads to a high level of sugar in your blood. Forxiga works by removing excess sugar from your body via your urine. If you have type 2 diabetes, it can also help prevent heart disease.

Forxiga and other diabetes medicines
Type 1 diabetes:
- Forxiga is used if your type 1 diabetes cannot be controlled with insulin alone.
- Forxiga is used together with insulin.

Type 2 diabetes:
- Forxiga is used if your type 2 diabetes cannot be controlled with diet and exercise.
- Your doctor may ask you to take Forxiga:
  - on its own – if you cannot tolerate metformin.
  - together with other medicines to treat diabetes.

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
Contact a doctor or the nearest hospital straight away:
- If you experience feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat or rapid weight loss.
- The above symptoms could be a sign of "diabetic ketoacidosis" – a serious, sometimes life-threatening problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests.
- The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness.
- When you are treated with Forxiga, diabetic ketoacidosis can occur even if your blood sugar is normal.
- The risk of getting diabetic ketoacidosis is different in the two types diabetes:
  - in type 2 diabetes it is rare.
  - in type 1 diabetes the risk is higher - this is because your body hardly produces any insulin, and diabetic ketoacidosis may occur at sudden decreases in insulin dose (such as missed insulin injections, or issues with your insulin pen or pump).

If you have type 1 diabetes:
- Talk with your doctor about the risk of diabetic ketoacidosis before you start to take Forxiga.
- Your doctor will tell you when you may need to measure ketones in your blood or urine and what you need to do when your ketone levels are raised:
  - At blood ketone readings from 0.6 to 1.5 mmol/L (or urine ketones reading +) you may need to take extra insulin, drink water, and if your blood glucose is normal or low, you may need to eat carbohydrates. Measure your ketone levels again in 2 hours. Seek medical advice immediately and stop taking Forxiga if levels persist and symptoms present.
  - At blood ketone readings over 1.5 to 3.0 mmol/L (or urine ketones reading ++) you may be developing diabetic ketoacidosis, seek medical advice immediately and stop taking Forxiga. You may need to take extra insulin, drink water, and if your blood glucose is normal or low, you may need to eat carbohydrates. Measure your ketone levels again in 2 hours.
  - At blood ketone readings over 3.0 mmol/L (or urine ketones reading +++) you probably have diabetic ketoacidosis, go to the emergency department without delay and stop taking Forxiga. You may need to take extra insulin, drink water, and if your blood glucose is normal or low, you may need to eat carbohydrates.

If you suspect you have diabetic ketoacidosis, contact a doctor or the nearest hospital straight away and do not take this medicine.

Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier's gangrene which destroys the tissue under the skin. Fournier's gangrene has to be treated immediately.

Talk to your doctor, pharmacist or nurse before taking Forxiga:
- if you have a kidney problem – your doctor may ask you to take a different medicine.
- if you have a liver problem.
- if you are on medicines to lower your blood pressure (anti-hypertensives) and have a history of low blood pressure (hypotension). More information is given below under 'Other medicines and Forxiga'.
- if you have very high levels of sugar 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. 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.

Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

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.
- if you have type 2 diabetes and 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 (hypoglycaemia).

If you are taking Forxiga for type 1 diabetes, it is important that you keep using insulin.

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 (hypoglycaemia), which may cause symptoms such as shaking, sweating and change in vision, and may affect your ability to drive and use machines.

Do not drive or use any tools or machines, if you feel dizzy 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, pharmacist or nurse if you are not sure.

How much to take
If you are taking Forxiga for type 2 diabetes:
- 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.

If you are taking Forxiga for type 1 diabetes:
- The recommended dose is one 5 mg tablet each day.

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 other medicine(s) to lower the amount of sugar in your blood. Remember to take these other medicine(s) as your doctor has told you. This will help get the best results for your health.

Diet and exercise can help your body use its blood sugar better. It is important to stay on any diet and exercise program recommended by your doctor while 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.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

- **angioedema,** seen very rarely (may affect up to 1 in 10,000 people).

These are signs of angioedema:
- swelling of the face, tongue or throat
- difficulties swallowing
- hives and breathing problems

- **diabetic ketoacidosis** - this is common in patients with type 1 diabetes (may affect up to 1 in 10 people) and rare in patients with type 2 diabetes (may affect up to 1 in 1,000 people).

These are the signs of diabetic ketoacidosis (see also section 2 Warnings and precautions):
- increased levels of "ketone bodies" in your urine or blood
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing
- confusion
- unusual sleepiness or tiredness
- a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat
- rapid weight loss.

This may occur regardless of blood sugar level. Your doctor may decide to temporarily or permanently stop your treatment with Forxiga.

- **necrotising fasciitis of the perineum** or Fournier's gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus, seen very rarely.

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 (may affect up to 1 in 100 people).

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 heartbeat.

- **urinary tract infection,** seen commonly (may affect up to 1 in 10 people).

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 (hypoglycaemia) - 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
- genital infection (thrush) of your penis or vagina (signs may include irritation, itching, unusual discharge or odour)
- 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)
- increases in the amount of red blood cells in your blood (shown in tests)
- decreases in creatinine renal clearance (shown in tests) in the beginning of treatment
- dizziness
- rash

Uncommon
- thirst
- constipation
- awakening from sleep at night to pass urine
- dry mouth
- weight decreased
- increases in creatinine (shown in laboratory blood tests) in the beginning of treatment
- increases in urea (shown in laboratory blood tests)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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.

- The other ingredients are:
  - tablet core: microcrystalline cellulose (E460i), lactose (see section 2 ‘Forxiga contains lactose’), crospovidone (E1202), 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 5 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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This leaflet was last revised in

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

Package leaflet: Information for the patient

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. See section 4.

What is in this leaflet:

1. What Forxiga is and what it is used for

What Forxiga is
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 in adult patients (aged 18 years and older).

What Forxiga is used for
Forxiga is used for the type of diabetes called type 2 diabetes – where your body does not make enough insulin or 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. It can also help prevent heart disease.

Forxiga and other diabetes medicines
Forxiga is used if your type 2 diabetes cannot be controlled with diet and exercise.

Your doctor may ask you to take Forxiga:
- on its own – if you cannot tolerate metformin.
- together with other medicines to treat diabetes.

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
Contact a doctor or the nearest hospital straight away:
- If you experience feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat or rapid weight loss.
- The above symptoms could be a sign of "diabetic ketoacidosis" – a serious, sometimes life-threatening problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests.
- The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness.
- When you are treated with Forxiga, diabetic ketoacidosis can occur even if your blood sugar is normal.

If you suspect you have diabetic ketoacidosis, contact a doctor or the nearest hospital straight away and do not take this medicine.

Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier's gangrene which destroys the tissue under the skin. Fournier's gangrene has to be treated immediately.

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 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 are on medicines to lower your blood pressure (anti-hypertensives) and have a history of low blood pressure (hypotension). More information is given below under 'Other medicines and Forxiga'.
- if you have very high levels of sugar 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. 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.

Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

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.
- if you have type 2 diabetes and 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 (hypoglycaemia).

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 (hypoglycaemia), which may cause symptoms such as shaking, sweating and change in vision, and may affect your ability to drive and use machines.

Do not drive or use any tools or machines, if you feel dizzy 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, pharmacist or nurse if you are not sure.

How much to take
If you are taking Forxiga for type 2 diabetes:
- 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 other medicine(s) to lower the amount of sugar in your blood. Remember to take these other medicine(s) as your doctor has told you. This will help get the best results for your health.

Diet and exercise can help your body use its blood sugar better. It is important to stay on any diet and exercise program recommended by your doctor while 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.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

- **angioedema,** seen very rarely (may affect up to 1 in 10,000 people).

These are signs of angioedema:
- swelling of the face, tongue or throat
- difficulties swallowing
- hives and breathing problems

- **diabetic ketoacidosis** - this is rare in patients with type 2 diabetes (may affect up to 1 in 1,000 people).

These are the signs of diabetic ketoacidosis (see also section 2 Warnings and precautions):
- increased levels of "ketone bodies" in your urine or blood
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing
- confusion
- unusual sleepiness or tiredness
- a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat
- rapid weight loss.

This may occur regardless of blood sugar level. Your doctor may decide to temporarily or permanently stop your treatment with Forxiga.

- **necrotising fasciitis of the perineum** or Fournier's gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus, seen very rarely.

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 (may affect up to 1 in 100 people).

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 heartbeat.

- **urinary tract infection,** seen commonly (may affect up to 1 in 10 people).

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 (hypoglycaemia) - 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
- genital infection (thrush) of your penis or vagina (signs may include irritation, itching, unusual discharge or odour)
- 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)
- increases in the amount of red blood cells in your blood (shown in tests)
- decreases in creatinine renal clearance (shown in tests) in the beginning of treatment
- dizziness
- rash

Uncommon
- thirst
- constipation
- awakening from sleep at night to pass urine
- dry mouth
- weight decreased
- increases in creatinine (shown in laboratory blood tests) in the beginning of treatment
- increases in urea (shown in laboratory blood tests)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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 10 mg film-coated tablet (tablet) contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.
- The other ingredients are:
  - tablet core: microcrystalline cellulose (E460i), lactose (see section 2 'Forxiga contains lactose'), crospovidone (E1202), 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 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 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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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu