ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Qtern 5 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains saxagliptin hydrochloride equivalent to 5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

Excipient with known effect

Each tablet contains 40 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light brown to brown, biconvex, 0.8 cm round, film-coated tablet, with "5/10" printed on one side, and "1122" printed on the other side, in blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Qtern, fixed dose combination of saxagliptin and dapagliflozin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Qtern do not provide adequate glycaemic control,
- when already being treated with the free combination of dapagliflozin and saxagliptin.

(See sections 4.2, 4.4, 4.5 and 5.1 for available data on combinations studied.)

4.2 Posology and method of administration

Posology

The recommended dose is one 5 mg saxagliptin/10 mg dapagliflozin tablet once daily (see sections 4.5 and 4.8).

Missed dose
If a dose is missed and it is ≥ 12 hours until the next dose, the dose should be taken. If a dose is missed and it is < 12 hours until the next dose, the missed dose should be skipped and the next dose taken at the usual time.

Special populations
Renal impairment
Qtern 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. It should also not be used in patients with end-stage renal disease (ESRD) (see sections 4.4, 4.8, 5.1 and 5.2).

No dose adjustment is recommended based on renal function.

Hepatic impairment
This medicinal product can be used in patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment should be evaluated prior to initiation and during treatment.
It is not recommended for use in patients with severe hepatic impairment (see section 4.4).

Elderly (≥ 65 years)
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 this medicinal product in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.

Method of administration

Qtern is taken orally once daily. It may be taken at any time of day with or without food. Tablet is to be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl peptidase-4 (DPP-4) inhibitor or to any sodium-glucose co-transporter 2 (SGLT2) inhibitor (see sections 4.4, 4.8 and 6.1).

4.4 Special warnings and precautions for use

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis; persistent, severe abdominal pain. If pancreatitis is suspected, this medicinal product should be discontinued; if acute pancreatitis is confirmed, it should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In post-marketing experience of saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis (see section 4.8).

Renal impairment

The glycaemic efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (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. This medicinal product should not be initiated in patients with a GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. The saxagliptin/dapagliflozin fixed dose combination 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 this medicinal product and at least yearly, thereafter (see sections 4.2, 4.8, 5.1 and 5.2).
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function persistently falls below GFR < 45 mL/min, treatment with this medicinal product should be discontinued.

Use in patients at risk for volume depletion and/or hypotension

Due to dapagliflozin's mechanism of action, this medicinal product 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 this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Use in patients with hepatic impairment

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin and saxagliptin exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2). The saxagliptin/dapagliflozin fixed dose combination can be used in patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment should be evaluated prior to initiation and during treatment. This medicinal product is not recommended for use in patients with severe hepatic impairment (see section 4.2).

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (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/litres (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of dapagliflozin.

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

In patients where DKA is suspected or diagnosed, treatment with this medicinal product should be discontinued immediately.

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

Before initiating treatment with this medicinal product, factors in the patient history that may predispose to ketoacidosis should be considered.

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

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

The safety and efficacy of the saxagliptin/dapagliflozin fixed dose combination in patients with type 1 diabetes have not been established and it should not be used for treatment of patients with type 1 diabetes. In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (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, Qtern should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Hypersensitivity reactions

This medicinal product must not be used in patients who have had any serious hypersensitivity reaction to a DPP-4 inhibitor or a SGLT2 inhibitor (see section 4.3).

During post-marketing experience with saxagliptin, including spontaneous reports and clinical trials, the following adverse reactions have been reported with the use of saxagliptin: serious hypersensitivity reactions, including anaphylactic reaction, anaphylactic shock, and angioedema. This medicinal product should be discontinued if a serious hypersensitivity reaction is suspected. The event should be assessed and alternative treatment for diabetes should be instituted (see section 4.8).

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of this medicinal product 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 monitoring of renal function apply to elderly patients as to all patients (see sections 4.2, 4.4, 4.8, and 5.1).

Therapeutic experience with this medicinal product in patients 65 years and older is limited, and very limited in patients 75 years and older.

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies with saxagliptin (see section 5.3). Skin lesions were not observed at an increased incidence in saxagliptin clinical trials. Post-marketing reports of rash have been described in the DPP-4

inhibitor class. Rash is also noted as an adverse reaction for this medicinal product (see section 4.8). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Bullous pemphigoid

Post-marketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP4 inhibitor use, including saxagliptin. In reported cases, patients typically responded to topical or systemic immunosuppressive treatment and discontinuation of the DPP4 inhibitor. If a patient develops blisters or erosions while receiving saxagliptin and bullous pemphigoid is suspected, this medicinal product should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (see section 4.8).

Cardiac failure

There is no experience in clinical trials with dapagliflozin in NYHA class IV. Experience in NYHA class III-IV is limited with saxagliptin.

In the SAVOR trial, a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin-treated patients compared to placebo, although a causal relationship has not been established (see section 5.1). Additional analysis did not indicate a differential effect among NYHA classes.

Caution is warranted if the saxagliptin/dapagliflozin fixed dose combination is used in patients who have known risk factors for hospitalisation for heart failure, such as a history of heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms.

Arthralgia

Joint pain, which may be severe, has been reported in post-marketing reports for DPP-4 inhibitors (see section 4.8). Patients experienced relief of symptoms after discontinuation of the medicinal product and some experienced recurrence of symptoms with reintroduction of the same or another DPP-4 inhibitor. Onset of symptoms following initiation of therapy may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of therapy should be individually assessed.

Immunocompromised patients

Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome have not been studied in the saxagliptin clinical programme. The efficacy and safety profile of the saxagliptin/dapagliflozin fixed dose combination in these patients has not been established.

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.

Use with medicinal products known to cause hypoglycaemia

Both saxagliptin and dapagliflozin can individually increase the risk of hypoglycaemia when combined with an insulin secretagogue. If this medicinal product is used in combination with insulin secretagogue (sulphonylurea), a reduction in the dose of sulphonylurea may be required to minimise the risk of hypoglycaemia (see section 4.8).

Urine laboratory assessments

Due to the mechanism of action of dapagliflozin, patients taking this medicinal product will test positive for glucose in their urine.

Use with potent CYP3A4 inducers

Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may reduce the glycaemic lowering effect of this medicinal product. Glycaemic control should be assessed when it is used concomitantly with a potent CYP3A4/5 inducer (see section 4.5).

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.

Sodium

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

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).

Use with medicinal products known to cause hypoglycaemia
If this medicinal product is used in combination with insulin secretagogue (sulphonylurea), a reduction in the dose of sulphonylurea may be required to minimise the risk of hypoglycaemia (see section 4.4).

Pharmacokinetic interactions

Saxagliptin: The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5).

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

Interactions with other oral anti-diabetic or cardiovascular medicinal products
Saxagliptin: Saxagliptin did not meaningfully alter the pharmacokinetics of dapagliflozin, metformin, glibenclamide, pioglitazone, digoxin, diltiazem or simvastatin. These medicinal products did not alter the pharmacokinetics of saxagliptin or its major active metabolite.

Dapagliflozin: Dapagliflozin did not meaningfully alter the pharmacokinetics of saxagliptin, metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. These medicinal products did not alter the pharmacokinetics of dapagliflozin.

Effect of other medicinal products on saxagliptin or dapagliflozin
Saxagliptin: Concomitant administration of saxagliptin with the moderate inhibitor of CYP3A4/5 diltiazem, increased the C_{max} and AUC of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44% and 34%, respectively. These pharmacokinetic effects are not clinically meaningful and do not require dose adjustment.

Concomitant administration of saxagliptin with the potent inhibitor of CYP3A4/5 ketoconazole, increased the C_{max} and AUC of saxagliptin by 62% and 2.5-fold, respectively, and the corresponding values for the active metabolite were decreased by 95% and 88%, respectively. These pharmacokinetic effects are not clinically meaningful and do not require dose adjustment.

Concomitant administration of saxagliptin with the potent CYP3A4/5 inducer rifampicin reduced C_{max} and AUC of saxagliptin by 53% and 76%, respectively. The exposure of the active metabolite and the plasma DPP-4 activity inhibition over a dose interval were not influenced by rifampicin (see section 4.4).

The coadministration of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) has not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycaemic control should be carefully assessed when saxagliptin is used concomitantly with a potent CYP3A4/5 inducer.

In studies conducted in healthy subjects, neither the pharmacokinetics of saxagliptin nor its major metabolite were meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine.

Dapagliflozin: 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.

Effect of saxagliptin or dapagliflozin on other medicinal products
Saxagliptin: Saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide (a CYP2C9 substrate), pioglitazone [a CYP2C8 (major) and CYP3A4 (minor) substrate], digoxin (a P-gp substrate), simvastatin (a CYP3A4 substrate), the active components of a combined oral contraceptive (ethinylestradiol and norgestimate), diltiazem or ketoconazole.

Dapagliflozin: In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone [a CYP2C8 (major) and CYP3A4 (minor) substrate], sitagliptin, glimepiride (a CYP2C9 substrate), 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of saxagliptin and dapagliflozin in pregnant women. Studies in animals with saxagliptin have shown reproductive toxicity at high doses (see section 5.3). Studies with

dapagliflozin 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, Qtern should not be used during pregnancy. If pregnancy is detected, treatment with Qtern should be discontinued.

Breast-feeding

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

Fertility

The effect of saxagliptin and dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. Effects on fertility were observed using saxagliptin in male and female rats at high doses producing overt signs of toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Qtern has no or negligible influence on the ability to drive and use machines. When driving or using machines, it should be taken into account that dizziness has been reported in studies with combined use of saxagliptin and dapagliflozin. In addition, patients should be alerted to the risk of hypoglycaemia if used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. sulphonylureas).

4.8 Undesirable effects

Summary of the safety profile of saxagliptin plus dapagliflozin

The combination of saxagliptin 5 mg and dapagliflozin 10 mg in 1 169 adults with type 2 diabetes mellitus (T2DM) and inadequate glycaemic control on metformin has been evaluated in three phase 3, randomised, double-blind, active/placebo-control, parallel group, multi-centre clinical trials for up to 52 weeks (see section 5.1). The pooled safety analysis comprised 3 treatment groups: saxagliptin plus dapagliflozin plus metformin (492 subjects), saxagliptin plus metformin (336 subjects), and dapagliflozin plus metformin (341 subjects). The safety profile of the combined use of saxagliptin plus dapagliflozin plus metformin was comparable to the adverse reactions identified for the respective mono-components.

The most frequently reported adverse reactions associated with Qtern are upper respiratory tract infections (very common), hypoglycaemia when used with SU (very common), and urinary tract infections (common). Diabetic ketoacidosis may occur rarely (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions are presented in table 1. The safety profile is based on the summarized data from the saxagliptin/dapagliflozin combination clinical trials pooled safety data, and also clinical trials, post-authorisation safety studies and post-marketing experience with the mono-components. The adverse reactions are listed by system organ class (SOC) and frequency. Frequency categories were defined according to 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. Compilation of reported adverse reactions

System organ class	Very common	Common[A]	Uncommon[B]	Rare	Very rare	Not known
Infections and infestations	Upper respiratory tract infection[1]	Urinary tract infection[2], vulvovaginitis, balanitis and related genital infection[3], gastroenteritis[D]	Fungal infection		Necrotising fasciitis of the perineum (Fournier's gangrene)[C,F,7]	
Immune system disorders			Hypersensitivity reactions[C]	Anaphylactic reactions including anaphylactic shock[C]		
Metabolism and nutrition disorders	Hypoglycaemia[D] (when used with SU)	Dyslipidaemia[4]	Volume depletion[F], thirst	Diabetic ketoacidosis[F,G,7]		
Nervous system disorders		Headache, dizziness				
Gastrointestinal disorders		Abdominal pain[C], diarrhoea, dyspepsia[D], gastritis[D], nausea[C], vomiting[D]	Constipation, dry mouth, pancreatitis[C]			
Skin and subcutaneous tissue disorders		Rash[5]	Dermatitis[C], pruritus[C], urticaria[C]	Angioedema[C]		Bullous pemphigoid[C,7]
Musculoskeletal and connective tissue disorders		Arthralgia, back pain, myalgia[D]				
Renal and urinary disorders		Dysuria, polyuria[D,6]	Nocturia			
Reproductive system and breast disorders			Erectile dysfunction, pruritus genital, vulvovaginal pruritus			
General disorders and administration site conditions		Fatigue[D], oedema peripheral[D]				
Investigations		Creatinine renal clearance decreased	Blood creatinine increased during initial			

System organ class	Very common	Common[A]	Uncommon[B]	Rare	Very rare	Not known
		during initial treatment[F], haematocrit increased[E]	treatment[F], blood urea increased, weight decreased			

[A] Adverse reactions reported in ≥ 2% of subjects treated with the combined use of saxagliptin + dapagliflozin in the pooled safety analysis, or if reported in < 2% in the pooled safety analysis, they were based on the individual mono-components data.
[B] Frequencies of all uncommon adverse reactions were based on the individual mono-components data.
[C] Adverse reaction originates from saxagliptin or dapagliflozin post-marketing surveillance data.
[D] Adverse reactions were reported in ≥ 2% of subjects with either mono-component and ≥ 1% more than placebo, but not in the pooled analysis.
[E] Haematocrit values > 55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.
[F] Frequency is based on events in the dapagliflozin clinical programme.
[G] Reported in the dapagliflozin cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.
[1] Upper respiratory tract infection includes the following preferred terms: nasopharyngitis, influenza, upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, pharyngitis bacterial, tonsillitis, acute tonsillitis, laryngitis, viral pharyngitis, and viral upper respiratory tract infection.
[2] Urinary tract infection includes the following preferred terms: urinary tract infection, *Escherichia* urinary tract infection, pyelonephritis, and prostatitis.
[3] Vulvovaginitis, balanitis and related genital infection include the following preferred terms: vulvovaginal mycotic infection, balanoposthitis, genital infection fungal, vaginal infection, and vulvovaginitis.
[4] Dyslipidaemia includes the following preferred terms: dyslipidaemia, hyperlipidaemia, hypercholesterolaemia, and hypertriglyceridaemia.
[5] Rash was reported during the post-marketing use of saxagliptin and dapagliflozin. Preferred terms reported in dapagliflozin clinical trials included in order of frequency: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous.
[6] Polyuria includes the following preferred terms: polyuria, and pollakiuria.
[7] See section 4.4
SU = sulphonylurea

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections
Saxagliptin/dapagliflozin combination: The reported adverse events of vulvovaginitis, balanitis and related genital infections from pooled safety analysis were reflective of the safety profile of dapagliflozin. Adverse events of genital infection were reported in 3.0% in the saxagliptin plus dapagliflozin plus metformin group, 0.9% of saxagliptin plus metformin group and 5.9% of subjects in the dapagliflozin plus metformin group. The majority of the genital infection adverse events were reported in females (84% of subjects with a genital infection), were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Cases of phimosis/acquired phimosis have been reported with dapagliflozin concurrent with genital infections and in some cases, circumcision was required.

Hypoglycaemia
In the pooled safety analysis, the overall incidence of hypoglycaemia (all reported events including those with central laboratory FPG ≤ 3.9 mmol/L) was 2.0% in subjects treated with saxagliptin 5 mg plus dapagliflozin 10 mg plus metformin (combination therapy), 0.6% in the saxagliptin plus metformin group, and 2.3% in the dapagliflozin plus metformin group.

In a 24-week study comparing the combination of saxagliptin and dapagliflozin plus metformin with or without SU, with insulin plus metformin with or without SU, the overall incidence rates for hypoglycaemia in patients without a background treatment of SU, were 12.7% for the combination compared to 33.1% for insulin. The overall incidence rates of hypoglycaemia in two 52-week studies

comparing the combination therapy to glimepiride (SU) were: for the 1st study, 4.2% for the combination therapy versus 27.9% for glimepiride plus metformin versus 2.9% for dapagliflozin plus metformin; for the 2nd study, 18.5% for the combination therapy versus 43.1% for glimepiride plus metformin.

Volume depletion
Saxagliptin/dapagliflozin combination: Events suggestive of volume depletion (hypotension, dehydration, and hypovolaemia) were reported in two subjects (0.4%) in the saxagliptin plus dapagliflozin plus metformin group (serious adverse event [SAE] of syncope and an AE of urine output decreased), and 3 subjects (0.9%) in the dapagliflozin plus metformin group (2 AEs of syncope and 1 of hypotension).

Events related to decreased renal function
Saxagliptin/dapagliflozin combination: In the pooled safety analysis, the incidence of adverse events related to decreased renal function was 2.0% subjects in the saxagliptin plus dapagliflozin plus metformin group, 1.8% subjects in the saxagliptin plus metformin group, and 0.6% subjects in the dapagliflozin plus metformin group. Subjects with adverse events of renal impairment had lower mean eGFR values at baseline of 61.8 mL/min/1.73m^2 compared to 93.6 mL/min/1.73m^2 in the overall population. The majority of events were considered non-serious, mild or moderate in intensity, and resolved. The change in mean eGFR from baseline at week 24 was -1.17 mL/min/1.73m^2 in the saxagliptin plus dapagliflozin plus metformin group, -0.46 mL/min/1.73 m^2 in saxagliptin plus metformin, and 0.81 mL/min/1.73m^2 in dapagliflozin plus metformin.

Dapagliflozin: Adverse reactions related to increased creatinine have been reported for dapagliflozin as a mono-component. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

Necrotising fasciitis of the perineum (Fournier's gangrene)
Cases of Fournier's gangrene have been reported post-marketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

In the dapagliflozin cardiovascular outcomes study (DECLARE) 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.

Diabetic ketoacidosis
In the dapagliflozin cardiovascular outcomes study (DECLARE), 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
Saxagliptin/dapagliflozin combination: In the pooled safety analysis, urinary tract infections (UTIs) were balanced across the 3 treatment groups: 5.7% in the saxagliptin plus dapagliflozin plus metformin group, 7.4% in the saxagliptin plus metformin group and 5.6% in the dapagliflozin plus metformin group. One patient in the saxagliptin plus dapagliflozin plus metformin group experienced an SAE of pyelonephritis and discontinued treatment. The majority of the urinary tract infection adverse events were reported in females (81% of subjects with UTI), were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Laboratory findings
Decrease in lymphocyte counts
Saxagliptin: In a pool of 5 placebo-controlled studies, a small decrease in absolute lymphocyte count was observed, approximately 100 cells/microl relative to placebo. Mean absolute lymphocyte counts

remained stable with daily dosing up to 102 weeks in duration. This decrease in mean absolute lymphocyte count was not associated with clinically relevant adverse reactions.

Lipids
Saxagliptin/dapagliflozin combination: Data from the saxagliptin plus dapagliflozin plus metformin treatment arms of 3 phase 3 trials, demonstrated trends of mean percent increases from baseline (rounded to the nearest tenth) in total cholesterol (Total C), (ranging from 0.4% to 3.8%), LDL-C (ranging from 2.1% to 6.9%) and HDL-C (ranging 2.3% to 5.2%) along with mean percent decreases from baseline in triglycerides (ranging from -3.0% to -10.8%).

Special populations

Elderly
Saxagliptin/dapagliflozin combination: Of the 1 169 subjects treated in the pooled safety data from the 3 clinical trials, 1 007 subjects (86.1%) were aged < 65 years, 162 subjects (13.9%) were aged ≥ 65 years, and 9 subjects (0.8%) were aged ≥ 75 years. Generally, the most common adverse events reported in ≥ 65 years old were similar to < 65 years old. Therapeutic experience in patients 65 years and older is limited, and very limited in patients 75 years and older.

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

There is no information available on overdose with the saxagliptin/dapagliflozin fixed dose combination. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Saxagliptin

Saxagliptin had no clinically meaningful effect on QTc interval or heart rate at oral doses up to 400 mg daily for 2 weeks (80 times the recommended dose). Saxagliptin and its major metabolite are removed by haemodialysis (23% of dose over four hours).

Dapagliflozin

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. The removal of dapagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD21

Mechanism of action

This medicinal product combines saxagliptin and dapagliflozin with complementary mechanisms of action to improve glycaemic control. Saxagliptin, through the selective inhibition of dipeptidyl peptidase-4 (DPP-4), enhances glucose-mediated insulin secretion (incretin effect). Dapagliflozin, a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2), inhibits renal glucose reabsorption independently of insulin. Actions of both medicinal products are regulated by the plasma glucose level.

Saxagliptin is a highly potent (K_i: 1.3 nM), selective, reversible and competitive inhibitor of DPP-4, an enzyme responsible for the breakdown of incretin hormones. This results in a glucose-dependent increase in insulin secretion, thus reducing fasting and post-prandial blood glucose concentrations.

Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). Dapagliflozin blocks reabsorption of filtered glucose from the S1 segment of the renal tubule, effectively lowering blood glucose in a glucose dependent and insulin-independent manner. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. The increased urinary glucose excretion with SGLT2 inhibition produces an osmotic diuresis, and can result in a reduction in systolic BP.

Pharmacodynamic effects

In patients with type 2 diabetes, administration of saxagliptin inhibited DPP-4 enzyme activity throughout a 24-hour period. The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site. After an oral glucose load, this produced in a 2- to 3-fold increase in circulating levels glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations, and increased beta-cell responsiveness, resulting in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic beta-cells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Dapagliflozin's glucuretic effect is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. 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. 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

The safety and efficacy of the 5 mg saxagliptin/10 mg dapagliflozin fixed-dose combination was evaluated in three phase 3, randomised, double-blind, active/placebo-controlled clinical trials in 1 169 adult subjects with type 2 diabetes mellitus. One trial with saxagliptin and dapagliflozin added

concomitantly to metformin was conducted for 24 weeks. Two add-on therapy trials, which added either dapagliflozin to saxagliptin plus metformin or saxagliptin to dapagliflozin plus metformin, were also conducted for 24 weeks followed by a 28 week extension treatment period. The safety profile of the combined use of saxagliptin plus dapagliflozin in these trials for up to 52 weeks was comparable to the safety profiles for the mono-components.

Glycaemic control

Concomitant therapy with saxagliptin and dapagliflozin in patients inadequately controlled on metformin

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone (HbA1c ≥ 8% and ≤ 12%), participated in this 24-week randomised, double-blind, active comparator-controlled superiority trial to compare the combination of saxagliptin and dapagliflozin added concurrently to metformin, versus saxagliptin (DPP-4 inhibitor) or dapagliflozin (SGLT2 inhibitor) added to metformin. Patients were randomised to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin, saxagliptin 5 mg and placebo added to metformin, or dapagliflozin 10 mg and placebo added to metformin.

The saxagliptin and dapagliflozin group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see table 2).

Table 2. HbA1c at week 24 in active-controlled study comparing the combination of saxagliptin and dapagliflozin added concurrently to metformin with either saxagliptin or dapagliflozin added to metformin

Efficacy parameter	**Saxagliptin 5 mg + dapagliflozin 10 mg + metformin N=179[2]**	**Saxagliptin 5 mg + metformin N=176[2]**	**Dapagliflozin 10 mg + metformin N=179[2]**
HbA1c (%) at week 24[1]			
Baseline (mean)	8.93	9.03	8.87
Change from baseline (adjusted mean[3]) (95% confidence interval [CI])	−1.47 (−1.62, −1.31)	−0.88 (−1.03, −0.72)	−1.20 (−1.35, −1.04)
Difference from saxagliptin + metformin (adjusted mean[3]) (95% CI)	−0.59[4] (−0.81, −0.37)	-	-
Difference from dapagliflozin + metformin (adjusted mean[3]) (95% CI)	−0.27[5] (−0.48, −0.05)	-	-

[1] LRM = Longitudinal repeated measures (using values prior to rescue).
[2] Randomised and treated patients.
[3] Least squares mean adjusted for baseline value.
[4] p-value < 0.0001.
[5] p-value=0.0166.

The majority of patients in this study had a baseline HbA1c of > 8% (see table 3). The combination of saxagliptin and dapagliflozin added to metformin consistently demonstrated greater reductions in HbA1c irrespective of baseline HbA1c compared with saxagliptin or dapagliflozin alone added to metformin. In a separate pre-specified subgroup analysis, mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values.

Table 3. HbA1c subgroup analysis by baseline HbA1c at week 24 in randomised subjects

Treatments	Adjusted mean change from baseline by baseline HbA1c		
	< 8.0%	**≥ 8% to < 9.0%**	**≥ 9.0%**
Saxagliptin + dapagliflozin + metformin Adjusted mean change from baseline (95% CI)	–0.80 (n=37) (–1.12, –0.47)	–1.17 (n=56) (–1.44, –0.90)	–2.03 (n=65) (–2.27, –1.80)
Saxagliptin + metformin Adjusted mean change from baseline (95% CI)	–0.69 (n=29) (–1.06, –0.33)	–0.51 (n=51) (–0.78, –0.25)	–1.32 (n=63) (–1.56, –1.09)
Dapagliflozin + metformin Adjusted mean change from baseline (95% CI)	–0.45 (n=37) (–0.77, –0.13)	–0.84 (n=52) (–1.11, –0.57)	–1.87 (n=62) (–2.11, –1.63)

n = number of subjects with non-missing baseline and a week 24 value.

Proportion of patients achieving HbA1c < 7%
Forty-one point four percent (41.4%) (95% CI [34.5, 48.2]) of patients in the saxagliptin and dapagliflozin combination group achieved HbA1c levels of less than 7% compared to 18.3% (95% CI [13.0, 23.5]) patients in the saxagliptin group and 22.2% (95% CI [16.1, 28.3]) patients in the dapagliflozin group.

Add-on therapy with dapagliflozin in patients inadequately controlled on saxagliptin plus metformin
A 24-week randomised, double-blind, placebo-controlled study compared the sequential addition of 10 mg dapagliflozin to 5 mg saxagliptin and metformin to the addition of placebo to 5 mg saxagliptin (DPP-4 inhibitor) and metformin in patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥ 7% and ≤ 10.5%). Three hundred twenty (320) subjects were randomised equally into either the dapagliflozin added to saxagliptin plus metformin treatment group or placebo plus saxagliptin plus metformin treatment group. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks).

The group with dapagliflozin sequentially added to saxagliptin and metformin achieved statistically significant (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to saxagliptin plus metformin group at 24 weeks (see table 4). The effect in HbA1c observed at week 24 was sustained at week 52.

Add-on therapy with saxagliptin in patients inadequately controlled on dapagliflozin plus metformin
A 24-week randomised, double-blind, placebo-controlled study conducted on patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥ 7% and ≤ 10.5%) on metformin and dapagliflozin alone, compared the sequential addition of 5 mg saxagliptin to 10 mg dapagliflozin and metformin, to the addition of placebo to 10 mg dapagliflozin and metformin, 153 patients were randomised into the saxagliptin added to dapagliflozin plus metformin treatment group, and 162 patients were randomised into the placebo added to dapagliflozin plus metformin treatment group. Patients who completed the initial 24-week study period were eligible to enter a controlled 28 week long-term study extension (52 weeks). The safety profile of saxagliptin added to dapagliflozin plus metformin in the long-term treatment period was consistent with that previously observed in the clinical trial experience for the concomitant therapy study and that observed in the 24-week treatment period in this study.

The group with saxagliptin sequentially added to dapagliflozin and metformin achieved statistically significant (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to dapagliflozin plus metformin group at 24 weeks (see table 4). The effect in HbA1c observed at week 24 was sustained at week 52.

Table 4. HbA1c change from baseline at week 24 excluding data after rescue for randomised subjects – studies MB102129 and CV181168

Efficacy parameter	Sequential add-on clinical trials			
	Study MB102129		Study CV181168	
	Dapagliflozin 10 mg add to saxagliptin 5 mg + metformin (N=160) †	Placebo + saxagliptin 5 mg + metformin (N=160) †	Saxagliptin 5 mg added to dapagliflozin 10 mg + metformin (N=153) †	Placebo + dapagliflozin 10 mg + metformin (N=162) †
HbA1c (%) at week 24 *				
Baseline (mean)	8.24	8.16	7.95	7.85
Change from baseline (adjusted mean‡) (95% CI)	−0.82 (−0.96, 0.69)	−0.10 (−0.24, 0.04)	−0.51 (−0.63, −0.39)	−0.16 (−0.28, −0.04)
Difference in HbA1c effect				
Adjusted mean (95% CI) p-value	−0.72 (−0.91, −0.53) < 0.0001		−0.35 (−0.52, −0.18) < 0.0001	

* LRM = Longitudinal repeated measures (using values prior to rescue).

† N is the number of randomised and treated patients.

‡ Least squares mean adjusted for baseline value.

Proportion of patients achieving HbA1c < 7%

The proportion of patients achieving HbA1c < 7.0% at week 24 in the add-on therapy with dapagliflozin to saxagliptin plus metformin trial was higher in the dapagliflozin plus saxagliptin plus metformin group 38.0% (95% CI [30.9, 45.1]) compared to the placebo plus saxagliptin plus metformin group 12.4% (95% CI [7.0, 17.9]). The effect in HbA1c observed at week 24 was sustained at week 52. The proportion of patients achieving HbA1c < 7% at week 24 for add-on therapy with saxagliptin to dapagliflozin plus metformin trial was higher in the saxagliptin plus dapagliflozin plus metformin group 35.3% (95% CI [28.2, 42.2]) compared to the placebo plus dapagliflozin plus metformin group 23.1% (95% CI [16.9, 29.3]). The effect in HbA1c observed at week 24 was sustained at week 52.

Body weight

In the concomitant study, the adjusted mean change from baseline in body weight at week 24 (excluding data after rescue) was −2.05 kg (95% CI [−2.52, −1.58]) in the saxagliptin 5 mg plus dapagliflozin 10 mg plus metformin group and −2.39 kg (95% CI [−2.87, −1.91]) in the dapagliflozin 10 mg plus metformin group, while the saxagliptin 5 mg plus metformin group had no change (0.00 kg) (95% CI [−0.48, 0.49]).

Blood pressure
Treatment with the saxagliptin/dapagliflozin fixed dose combination resulted in change from baseline for systolic blood pressure ranging from –1.3 to –2.2 mmHg and for diastolic blood pressure ranging from –0.5 to –1.2 mmHg caused by its mild diuretic effect. The modest lowering effects on BP were consistent over time and a similar number of subjects had systolic BP < 130 mmHg or diastolic BP < 80 mmHg at week 24 across the treatment groups.

Cardiovascular safety
In the pool of three studies, cardiovascular (CV) events that were adjudicated and confirmed as CV events were reported in a total of 1.0% of subjects in the saxagliptin plus dapagliflozin plus metformin group, 0.6% in the saxagliptin plus metformin group, and 0.9% in the dapagliflozin plus metformin group.

Cardiovascular outcomes studies in patients with type 2 diabetes mellitus
No cardiovascular outcomes studies have been conducted to evaluate the saxagliptin/dapagliflozin combination.

Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus - thrombolysis in myocardial infarction (SAVOR) study
SAVOR was a CV outcome trial in 16 492 patients with HbA1c ≥ 6.5% and < 12% (12,959 with established CV disease; 3 533 with multiple risk factors only) who were randomised to saxagliptin (n=8 280) or placebo (n=8 212) added to regional standards of care for HbA1c and CV risk factors. The study population included those ≥ 65 years (n=8 561) and ≥ 75 years (n=2 330), with normal or mild renal impairment (n=13 916) as well as moderate (n=2 240) or severe (n=336) renal impairment.

The primary safety (non-inferiority) and efficacy (superiority) endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke.

After a mean follow up of 2 years, the trial met its primary safety endpoint demonstrating saxagliptin does not increase the cardiovascular risk in patients with type 2 diabetes compared to placebo when added to current background therapy.

No benefit was observed for MACE or all-cause mortality.

One component of the secondary composite endpoint, hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance favouring placebo [HR=1.27; (95% CI 1.07, 1.51); P=0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at higher risk for hospitalisation for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.

Another secondary endpoint, all-cause mortality, occurred at a rate of 5.1% in the saxagliptin group and 4.6% in the placebo group. CV deaths were balanced across the treatment groups. There was a numerical imbalance in non-CV death, with more events on saxagliptin (1.8%) than placebo (1.4%) [HR=1.27; (95% CI 1.00, 1.62); P=0.051].

Dapagliflozin Effect on Cardiovascular Events (DECLARE)
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%).

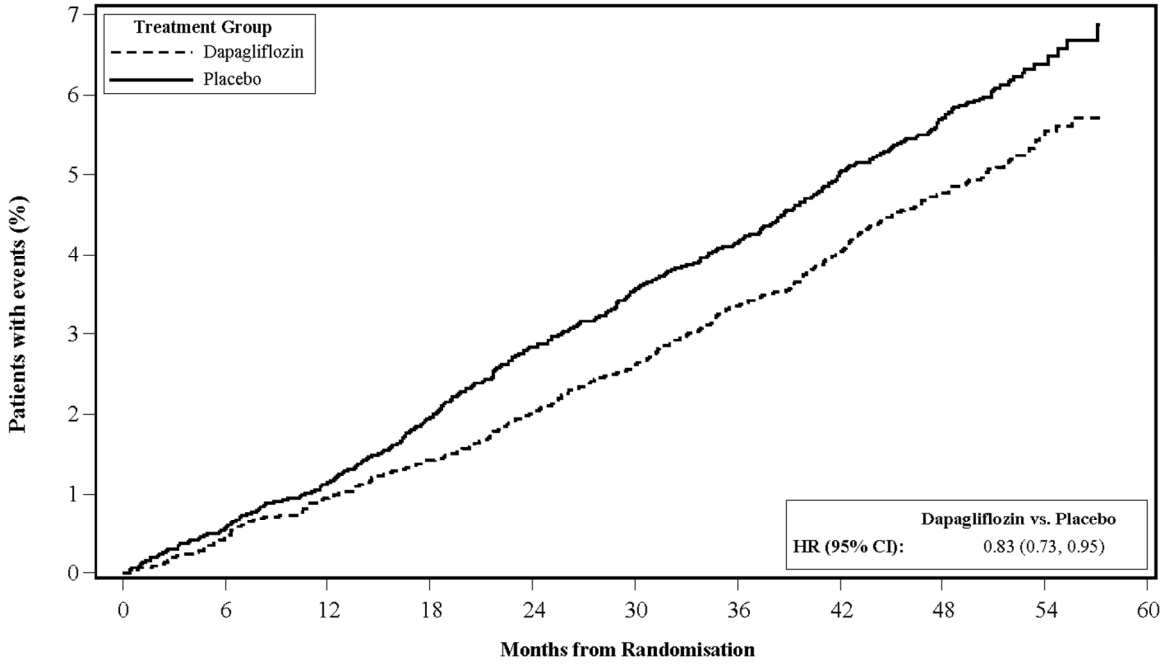
The primary endpoints were time to first event of the composite of cardiovascular death, myocardial infarction or ischaemic stroke (MACE) and time to first event of the composite of hospitalisation for heart failure or cardiovascular death. The secondary endpoints were a renal composite endpoint and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



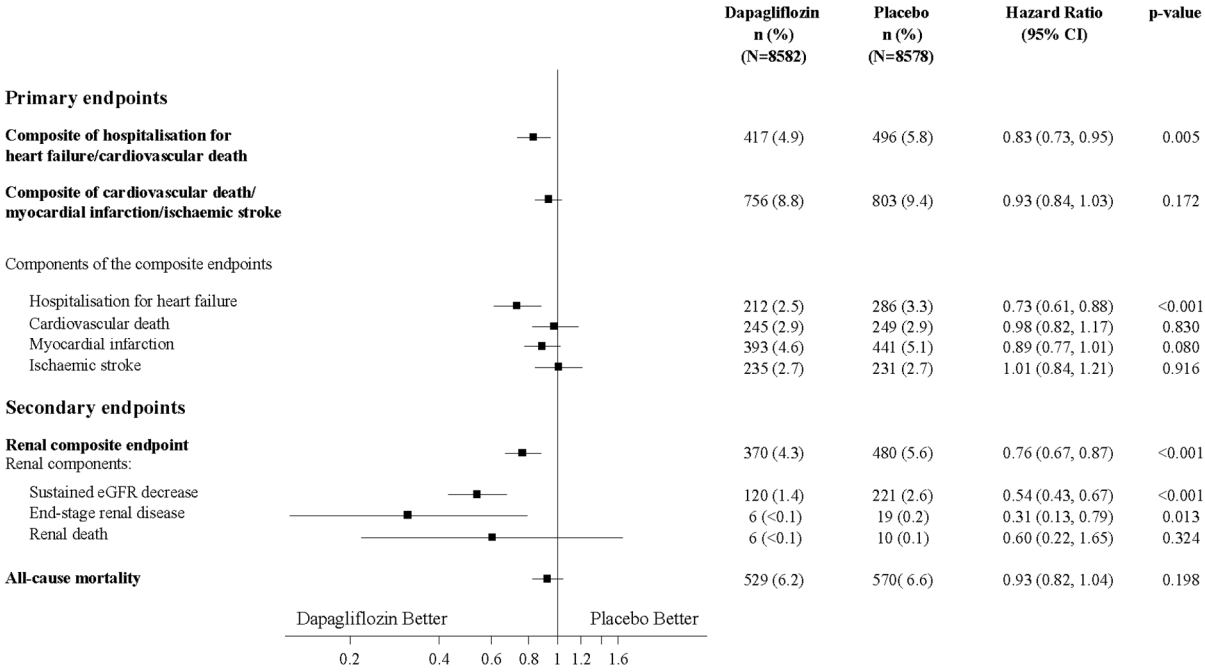
Patients at risk

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



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.

Renal impairment
Moderate renal impairment CKD 3A (eGFR ≥ 45 to < 60 mL/min/1.73 m^2)
Dapagliflozin

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 5).

Table 5. 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
* $p \leq 0.001$

At week 24, treatment with dapagliflozin demonstrated reductions in fasting plasma glucose (FPG) −1.19 mmol/L (−21.46 mg/dL) compared to −0.27 mmol/L (−4.87 mg/dL) for placebo ($p \leq 0.001$), and reductions in seated systolic blood pressure (SBP) −4.8 mmHg compared to −1.7 mmHg for placebo ($p < 0.05$).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Qtern in all 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

Saxagliptin/dapagliflozin combination: Overall, the pharmacokinetics of saxagliptin and dapagliflozin were not affected in clinically relevant manner when administered as a fixed dose combination compared with independent doses of saxagliptin and dapagliflozin.

The following reflects the pharmacokinetic properties of the saxagliptin/dapagliflozin fixed dose combination unless stated that the presented data are from administration of saxagliptin or dapagliflozin.

Bioequivalence has been confirmed between the Qtern 5 mg/10 mg tablet and the individual saxagliptin 5 mg and dapagliflozin 10 mg tablets after single dose administration in the fasted state in healthy subjects. The pharmacokinetics of dapagliflozin, and saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Administration of the saxagliptin/dapagliflozin fixed dose combination with a high-fat meal decreases dapagliflozin C_{max} by up to 35% and prolongs T_{max} by approximately 1.5 hours, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. There was no food effect observed for saxagliptin. This medicinal product can be administered with or without food.

Interactions with other medicinal products

Saxagliptin/dapagliflozin combination: No interaction studies have been performed with the saxagliptin/dapagliflozin fixed dose combination and other medicinal products. Such studies have been conducted with the individual active substances.

Saxagliptin: In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4.

Dapagliflozin: 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.

Absorption

Saxagliptin: Saxagliptin was rapidly absorbed after oral administration in the fasted state, with maximum plasma concentrations (C_{max}) of saxagliptin and its major metabolite attained within 2 and 4 hours (T_{max}), respectively. The C_{max} and AUC values of saxagliptin and its major metabolite increased proportionally with the increment in the saxagliptin dose, and this dose-proportionality was observed in doses up to 400 mg. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its major metabolite were 78 ng h/mL and 214 ng h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12%.

Dapagliflozin: 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%.

Distribution

Saxagliptin: The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is negligible. Thus, changes in blood protein levels in various disease states (e.g. renal or hepatic impairment) are not expected to alter the disposition of saxagliptin. The volume of distribution of saxagliptin was 205 L.

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

Biotransformation

Saxagliptin: The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major active metabolite of saxagliptin, 5-OH-saxagliptin, is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

Dapagliflozin: 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

Saxagliptin: The mean plasma terminal half-life ($t_{1/2}$) values for saxagliptin and its major metabolite are 2.5 hours and 3.1 hours respectively, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion.

Dapagliflozin: 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.

Linearity

Saxagliptin: The C_{max} and AUC of saxagliptin and its major metabolite increased proportionally to the saxagliptin dose. No appreciable accumulation of either saxagliptin or its major metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg.

Dapagliflozin: 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
Saxagliptin: After a single dose of saxagliptin in subjects with mild, moderate or severe renal impairment (or ESRD) classified on the basis of creatinine clearance the mean AUC values of

saxagliptin were 1.2-, and up to 2.1- and 4.5- fold higher, respectively, than AUC values in subjects with normal renal function. The AUC values of 5-OH-saxagliptin were also increased. The degree of renal impairment did not affect the C_{max} of saxagliptin or its major metabolite.

Dapagliflozin: 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
Saxagliptin: In subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe (Child-Pugh class C) hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to BMS-510849 (saxagliptin metabolite) were 22%, 7% and 33% lower, respectively, than those observed in healthy subjects.

Dapagliflozin: 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
Saxagliptin: Elderly patients (65–80 years) had about 60% higher saxagliptin AUC than young patients (18–40 years). This is not considered clinically meaningful, therefore, no dose adjustment for saxagliptin is recommended on the basis of age alone.

Dapagliflozin: 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.

Gender
Saxagliptin: Females had approximately 25% higher systemic exposure values for saxagliptin. There were no clinically relevant differences observed in saxagliptin pharmacokinetics between males and females.

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

Race
Saxagliptin: Race was not identified as a statistically significant covariate on the apparent clearance of saxagliptin and its metabolite.

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

Body weight
Saxagliptin: Body weight had a small and non-clinically meaningful impact on saxagliptin exposure. Females had approximately 25% higher systemic-exposure values for saxagliptin, this difference is considered not clinically relevant.

Dapagliflozin: 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 studies of either saxagliptin or dapagliflozin revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity or carcinogenicity.

Saxagliptin produced reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) in cynomolgus monkeys. The no effect level (NOEL) for the lesions is 1 and 2 times the human exposure of saxagliptin and the major metabolite respectively, at the recommended human dose (RHD) of 5 mg/day. The clinical relevance of the skin lesions is not known and skin lesions have not been observed in humans.

Immune related findings of minimal, nonprogressive, lymphoid hyperplasia in spleen, lymph nodes and bone marrow with no adverse sequelae have been reported in all species tested at exposures starting from 7 times the RHD.

Saxagliptin produced gastrointestinal toxicity in dogs, including bloody/mucoid faeces and enteropathy at higher doses with a NOEL 4 and 2 times the human exposure for saxagliptin and the major metabolite, respectively at RHD. The effect on offspring body weights were noted until postnatal day 92 and 120 in females and males, respectively.

<u>Reproductive and developmental toxicity</u>

Saxagliptin has effects on fertility in male and female rats at high doses producing overt signs of toxicity. Saxagliptin was not teratogenic at any doses evaluated in rats or rabbits. At high doses in rats, saxagliptin caused reduced ossification (a developmental delay) of the foetal pelvis and decreased foetal body weight (in the presence of maternal toxicity), with a NOEL 303 and 30 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (NOEL 158 and 224 times the human exposure for saxagliptin and the major metabolite, respectively at RHD). In a pre- and postnatal developmental study in rats, saxagliptin caused decreased pup weight at maternally toxic doses, with NOEL 488 and 45 times the human exposure for saxagliptin and the major metabolite, respectively at RHD. The effect on offspring body weights were noted until postnatal day 92 and 120 in females and males, respectively.

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (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 study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations (with dose-related increases in kidney weight and macroscopic kidney enlargement) were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

Dapagliflozin dosed to maternal rats from gestation day 6 through postnatal day 21, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (at maternal and pup dapagliflozin exposures of 1 415 times and 137 times, respectively, the human values at the maximum recommended human dose [MRHD]). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (pup exposures ≥ 29 times the human values at the MRHD). Maternal toxicity was evident only at the

highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The NOAEL for developmental toxicity is associated with a maternal systemic exposure 19 times the human values at the MRHD.

In studies of embryo-foetal development in rabbits, dapagliflozin caused neither maternal nor developmental toxicities at any dose tested; the highest dose tested corresponded to a systemic exposure 1 191 times the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1 441 times the human values at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460i)
Croscarmellose sodium (E468)
Lactose
Magnesium stearate (E470b)
Dental type silica (E551)

Film-coating

Poly(vinyl alcohol) (E1203)
Macrogol (3350)
Titanium dioxide (E171)
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)

Printing ink

Shellac
Indigo carmine aluminium lake (E132)

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

PA/Alu/PVC-Alu blister
Pack sizes of 14, 28, and 98 film-coated tablets in calendar blisters
Pack size of 30 film-coated tablets in blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1108/001 14 film-coated tablets
EU/1/16/1108/002 28 film-coated tablets
EU/1/16/1108/003 98 film-coated tablets
EU/1/16/1108/004 30 film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 July 2016
Date of latest renewal: 19 May 2021

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 AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Qtern 5 mg/10 mg film-coated tablets
saxagliptin/dapagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains saxagliptin hydrochloride equivalent to 5 mg saxagliptin and 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

film-coated tablets

14 film-coated tablets
28 film-coated tablets
98 film-coated tablets
30 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/1/16/1108/001 14 film-coated tablets
EU/1/16/1108/002 28 film-coated tablets
EU/1/16/1108/003 98 film-coated tablets
EU/1/16/1108/004 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

qtern 5 mg/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

1. NAME OF THE MEDICINAL PRODUCT

Qtern 5 mg/10 mg tablets
saxagliptin/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

1. NAME OF THE MEDICINAL PRODUCT

Qtern 5 mg/10 mg tablets
saxagliptin/dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Qtern 5 mg/10 mg film-coated tablets
saxagliptin/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 Qtern is and what it is used for

Qtern contains the active substances saxagliptin and dapagliflozin. Each belongs to a group of medicines called "oral anti-diabetics". These medicines are taken by mouth for diabetes.

Qtern is used for a type of diabetes called "type 2 diabetes mellitus" in adult patients (aged 18 years and older). If you have type 2 diabetes, your pancreas does not make enough insulin or your body is not able to use the insulin it produces properly. This leads to a high level of sugar in your blood. The two active substances in Qtern work in different ways to help control the level of sugar in your blood and remove excess sugar from your body via your urine.

Qtern is used to treat type 2 diabetes when:
- saxagliptin or dapagliflozin alone together with metformin and/or sulphonylurea cannot control your diabetes.
- you are already being treated with saxagliptin and dapagliflozin as single tablets. Your doctor may ask you to switch to this medicine.

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 Qtern

Do not take Qtern:
- if you are allergic to saxagliptin, dapagliflozin or any of the other ingredients of this medicine (listed in section 6).
- if you have had a serious allergic reaction to any other similar medicines (for example DPP-4 inhibitors like sitagliptin, linagliptin, alogliptin, or SGLT2 inhibitors like canagliflozin, empagliflozin) that you take to control your blood sugar.

Do not take Qtern if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist, or nurse before taking this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Qtern, and during treatment:
- if you have or have had a disease of the pancreas called pancreatitis. Possible signs of pancreatitis are listed in section 4.
- if you are on medicines to lower your blood pressure (anti-hypertensives) and have a history of low blood pressure (hypotension). For more information, see section "Other medicines and Qtern" below.
- 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 Qtern 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 Qtern until you recover to prevent dehydration.
- if you have moderate or severe liver problem.
- if you experience rapid weight loss, 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, contact a doctor or the nearest hospital straight away. These symptoms could be a sign of "diabetic ketoacidosis" – a rare but 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.
- if you have "type 1 diabetes" your body does not produce any insulin. Qtern should not be used to treat this condition.
- if you have or have had a serious hypersensitivity (allergic) reaction or is suspected. Signs of a serious allergic reaction are listed in section 4.
- if you often get infections of the urinary tract.
- if you have a history of serious heart disease.
- if you suffer from heart failure or you have other risk factors for developing heart failure such as problems with your kidneys. Your doctor will advise you of the signs and symptoms of heart failure. Symptoms can include, but are not limited to, increasing shortness of breath, rapid increase in weight and swelling of the feet (pedal oedema). You should call your doctor, pharmacist or nurse immediately if you experience any of these symptoms.
- if you have severe joint pain.
- if your body's ability to fight infections is reduced, for example if you have a disease like AIDS or have undergone an organ transplant.
- if you are taking a medicine to lower your blood sugar, such as sulphonylureas (see "Other medicines and Qtern").

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

Diabetic skin lesions (skin damage such as sores or ulcers) are a common complication of diabetes. Rash has been seen with both saxagliptin and dapagliflozin when given separately (see section 4). You are advised to follow the recommendations for skin care that you are given by your doctor or nurse. Contact your doctor if you encounter blistering of the skin, as it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Qtern.

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.

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.

Kidney function
Your kidneys should be checked before you start taking Qtern. During treatment with this medicine, your doctor will check your kidney function once a year or more frequently if you have worsening kidney function.

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

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

Other medicines and Qtern
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 increase the amount of water you pass out of the body (diuretic). Your doctor may ask you to stop taking Qtern. Possible signs of losing too much fluid from your body are listed at the top of section 4.
- if you are taking another medicine that lowers the amount of sugar in your blood such as a sulphonylurea (for example glimepiride). Your doctor may want to lower the dose of this other medicine, to prevent you from getting low blood sugar levels (hypoglycaemia).
- if you are using medicines containing any of the following active substances, that might have an effect on the breakdown of Qtern in your body. Your doctor may ask you to check your blood sugar levels more often while taking these medicines.
    - Carbamazepine, phenobarbital or phenytoin. These may be used to control fits (seizures) or chronic pain.
    - Dexamethasone – a steroid medicine. This may be used to treat inflammation in different body parts and organs.
    - Rifampicin. This is an antibiotic used to treat infections such as tuberculosis.
    - Ketoconazole. This may be used to treat fungal infections.
    - Diltiazem. This is a medicine used to treat angina (chest pain) and lower blood pressure.

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

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. Qtern is not recommended during pregnancy and your doctor will ask you to stop taking this medicine if you become pregnant. Talk to your doctor about the best way to control your blood sugar while you are pregnant.

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

Driving and using machines
Qtern is not expected to affect you being able to drive a car or use any tools or machines. If you feel dizzy while taking this medicine, do not drive or use any tools or machines. Taking this medicine together with another medicine that lowers your blood sugar, such as a sulphonylurea, can cause too low blood sugar levels (hypoglycaemia). This may cause symptoms such as shaking, sweating and change in vision, and may affect your ability to drive and use machines.

Qtern contains lactose
Qtern 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.

Qtern contains sodium

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

3. How to take Qtern

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
- The recommended dose is one tablet a 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 other medicines to lower the amount of sugar in your blood. Remember to take other medicine(s) as your doctor has told you. This will help get the best results for your health.

Diet and exercise
To control your diabetes, you still need to keep to diet and exercise, even when you are taking this medicine. So it is important to keep following the advice about diet and exercise from your doctor, pharmacist or nurse. In particular, if you are following a diabetic weight control diet, continue to follow it while you are taking Qtern.

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

If you forget to take Qtern
What to do if you forget to take a tablet.
- If it is less than 12 hours since you should have taken your dose, take a dose of Qtern as soon as you remember. Then take your next dose at the usual time.
- If it is more than 12 hours since you should have taken your dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose of Qtern to make up for a forgotten dose.

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

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

4. Possible side effects

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

Stop taking Qtern and see a doctor straight away if you notice any of the following serious side effects:

- **Symptoms of a serious allergic reaction (anaphylactic reaction, angioedema)** seen rarely, (may affect up to 1 in 1 000 people), which may include:
  - rash,
  - raised red patches on your skin (hives),
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or

swallowing.
Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

- **Pancreatitis**, seen uncommonly (may affect up to 1 in 100 people): severe and persistent pain in the abdomen (stomach area) which might reach through to your back, as well as nausea and vomiting, as it could be a sign of an inflamed pancreas.

- **Dehydration, (loss of too much fluid from your body)**, seen uncommonly.
  These are signs of dehydration:
  - very dry or sticky mouth, feeling very thirsty,
  - feeling very sleepy or tired,
  - passing little or no water (urine),
  - fast heart beat.

- **Urinary tract infection**, seen commonly (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.

- **Low blood sugar levels (hypoglycaemia)**, seen very commonly (may affect more than 1 in 10 people) if used with other diabetes medicines known to cause hypoglycaemia.
  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.

- **Diabetic ketoacidosis**, seen rarely.
  These are the signs of diabetic ketoacidosis (see also section 2 Warnings and precautions):
  - increased levels of "ketone bodies" in your urine or blood,
  - rapid weight loss,
  - 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.

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

- **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 (may affect up to 1 in 10 000 people).

Stop taking Qtern and see a doctor or nurse straight away, if you notice any of the serious side effects above.

Other side effects when taking Qtern alone or in combination with metformin:
Very common
- upper respiratory tract infection including:
  - infection of the upper chest or lungs,

- infection of the sinuses with a feeling of pain and fullness behind your cheeks and eyes (sinusitis),
- inflamed nose or throat (nasopharyngitis) (signs of this may include a cold or a sore throat).

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
- tiredness
- severe joint pain (arthralgia)
- stomach ache and indigestion (dyspepsia)
- nausea
- diarrhoea
- inflamed stomach or gut usually caused by an infection (gastroenteritis)
- headache, muscle pain (myalgia)
- vomiting, inflammation of the stomach (gastritis)
- 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)
- skin rash that may include raised bumps, skin irritation, or unpleasant itchiness
- difficulties in getting or maintaining an erection (erectile dysfunction)
- fungal infection
- hypersensitivity reactions
- itching in the genital area (pruritus genital or vulvovaginal pruritus) or discomfort while urinating

Not known (frequency cannot be estimated from the available data)
- blistering of the skin (bullous pemphigoid)

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 Qtern

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 and 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 Qtern contains
- The active substances are saxagliptin and dapagliflozin.
  Each tablet contains saxagliptin hydrochloride equivalent to 5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.
- The other ingredients are:
  - tablet core: microcrystalline cellulose (E460i), croscarmellose sodium (E468) (see section 2 'Qtern contains sodium'), lactose (see section 2 'Qtern contains lactose'), magnesium stearate (E470b), dental type silica (E551).
  - film-coating: poly(vinyl alcohol) (E1203), macrogol (3350), titanium dioxide (E171), talc (E553b), yellow iron oxide (E172), red iron oxide (E172).
  - printing ink: shellac, indigo carmine aluminium lake (E132).

What Qtern looks like and contents of the pack
Qtern 5 mg/10 mg film-coated tablets are light brown to brown, biconvex, 0.8 cm round, film-coated tablets, with "5/10" printed on one side, and "1122" printed on the other side, in blue ink.

Qtern 5 mg/10 mg tablets are available in aluminium blisters in pack sizes of 14, 28, or 98 film-coated tablets in calendar blisters and 30 film-coated tablets in blister.

Not all pack sizes may be marketed in your country.

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Manufacturer
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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