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 (as anhydrous).

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).

Special populations
Renal impairment
Qtern can be used in patients with mild renal impairment.

This medicinal product should not be used in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m², see sections 4.4, 4.8, 5.1 and 5.2). It should also not be used in patients with end-stage renal disease (ESRD) (see section 4.4, 4.8, and 5.2).
**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**
There is no restriction based solely on age. However, renal function and risk of volume depletion should be taken into account in elderly patients (≥ 65 years). Based on very limited experience in patients 75 years and older, initiation of Qtern therapy is not recommended in this population (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.

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.

**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**
**General**
Qtern should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoadidosis.

**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.

**Monitoring of renal function**
The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m²), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo. Qtern should not be used in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m²). This medicinal product has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m²) 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 falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m$^2$, Qtern treatment should be discontinued.

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

This medicinal product is not recommended for use in patients at risk of volume depletion (e.g. receiving loop diuretics) (see section 4.5) or who are volume depleted, e.g. due to acute illness (such as acute gastrointestinal illness with nausea, vomiting or diarrhoea).

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

For patients receiving Qtern, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with 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). Qtern 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 cases, have been reported in clinical trials and post-marketing 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 Qtern should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with dapagliflozin may be restarted once the patient’s condition has stabilised.

Before initiating Qtern, 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 dapagliflozin in patients with type 1 diabetes have not been established and Qtern should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials with dapagliflozin suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

**Hypersensitivity reactions**
Qtern 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. Qtern 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**
In the pooled safety data, urinary tract infections were frequently reported 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 at 52 weeks (see section 4.8). Additionally, urinary tract infections were frequently reported in saxagliptin and dapagliflozin clinical programmes.

**Urosepsis and pyelonephritis**
There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving dapagliflozin and other SGLT2 inhibitors. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Patients with signs and symptoms of urinary tract infections should be evaluated and promptly treated, if indicated (see section 4.8).

**Elderly**
Elderly patients are more likely to have impaired renal function, and may be at a greater risk for volume depletion. In addition, elderly patients are more likely to be treated with anti-hypertensive medicinal products that may cause volume depletion and/or changes in renal function [e.g. angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB)]. Therefore, renal function and risk of volume depletion should be taken into account prior to starting treatment with Qtern. 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).

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

Therapeutic experience with Qtern in patients 65 years and older is limited, and very limited in patients 75 years and older. Initiation of this medicinal product’s therapy in this population (> 75 years) is not recommended (see sections 4.2, 4.8, and 5.2).
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.

Cardiac failure
Experience in NYHA class I-II is limited in dapagliflozin. There is no experience in clinical trials with dapagliflozin in NYHA class III-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 Qtern is used in patients who have known risk factors for hospitalization 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.

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

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 Qtern in these patients has not been established.

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

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 Qtern is used in combination with insulin secretagogue (sulphonylurea), a reduction in the dose of sulphonylurea may be required to minimize the risk of hypoglycaemia (see section 4.8).

Urine laboratory assessments
Due to its mechanism of action, patients taking Qtern 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 Qtern. 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 anhydrous. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics
Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Use with medicinal products known to cause hypoglycaemia
If Qtern is used in combination with insulin secretagogue (sulphonylurea), a reduction in the dose of sulphonylurea may be required to minimize 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 medications 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\text{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\text{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\text{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.

**Other interactions**

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of saxagliptin, dapagliflozin or fixed dose combination tablet have not been studied.

**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 alternative methods to monitor glycaemic control.

### 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 1169 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 incidence of hypoglycaemia was low (1.4 %) in subjects treated with saxagliptin plus dapagliflozin plus metformin group. No episodes of major hypoglycaemia were reported, and no subject discontinued the study treatment due to hypoglycaemia.

Tabulated list of adverse reactions

The adverse reactions of Qtern are presented in table 1 based on the summarized data from the saxagliptin/dapagliflozin combination clinical trials pooled safety data. 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 (≥ 1/1000 to < 1/100), and rare (≥ 1/10,000 to < 1/1000).

Table 1. Compilation of reported adverse reactions for Qtern

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common</th>
<th>Common&lt;sup&gt;A&lt;/sup&gt;</th>
<th>Uncommon&lt;sup&gt;B&lt;/sup&gt;</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Urinary tract infection&lt;sup&gt;2&lt;/sup&gt;, vulvovaginitis, balanitis and related genital infection&lt;sup&gt;3&lt;/sup&gt;, gastroenteritis&lt;sup&gt;D&lt;/sup&gt;</td>
<td>Fungal infection</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity reactions&lt;sup&gt;C&lt;/sup&gt;</td>
<td></td>
<td>Anaphylactic reactions including anaphylactic shock&lt;sup&gt;E&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypoglycaemia&lt;sup&gt;D&lt;/sup&gt; (when used with SU)</td>
<td>Dyslipidaemia&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Volume depletion&lt;sup&gt;F&lt;/sup&gt;, thirst</td>
<td>Diabetic ketoacidosis&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td></td>
<td>Abdominal pain&lt;sup&gt;1&lt;/sup&gt;, diarrhoea, dyspepsia&lt;sup&gt;D&lt;/sup&gt;, gastritis&lt;sup&gt;D&lt;/sup&gt;, nausea&lt;sup&gt;C&lt;/sup&gt;, Constipation, dry mouth, pancreatitis&lt;sup&gt;C&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>System organ class</td>
<td>Very common</td>
<td>Common&lt;sup&gt;A&lt;/sup&gt;</td>
<td>Uncommon&lt;sup&gt;B&lt;/sup&gt;</td>
<td>Rare</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------</td>
<td>--------------------</td>
<td>----------------------</td>
<td>------</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Dysuria, polyuria&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Nocturia, renal impairment&lt;sup&gt;C&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash&lt;sup&gt;D&lt;/sup&gt;</td>
<td>Dermatitis&lt;sup&gt;C&lt;/sup&gt;, pruritus&lt;sup&gt;C&lt;/sup&gt;, urticaria&lt;sup&gt;C&lt;/sup&gt;</td>
<td>Angioedema&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Musculo-skeletal and connective tissue disorders</td>
<td>Arthralgia, back pain, myalgia&lt;sup&gt;B&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Erectile dysfunction, pruritus genital, vulvovaginal pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Fatigue&lt;sup&gt;B&lt;/sup&gt;, oedema peripheral&lt;sup&gt;B&lt;/sup&gt;</td>
<td>Blood creatinine increased&lt;sup&gt;F&lt;/sup&gt;, blood urea increased, weight decreased</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Creatinine renal clearance decreased&lt;sup&gt;E&lt;/sup&gt;, haematocrit increased&lt;sup&gt;E&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>A</sup> 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.

<sup>B</sup> Frequencies of all uncommon adverse reactions were based on the individual mono-components data.

<sup>C</sup> Adverse reaction originates from saxagliptin or dapagliflozin post-marketing surveillance data.

<sup>D</sup> Adverse reactions were reported in ≥ 2 % of subjects with either mono-component and ≥ 1 % more than placebo, but not in the pooled analysis.

<sup>E</sup> Haematocrit values > 55 % were reported in 1.3 % of the subjects treated with dapagliflozin 10 mg versus 0.4 % of placebo subjects.

<sup>F</sup> See corresponding subsections below for events in the dapagliflozin programme.

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 Polyuria includes the following preferred terms: polyuria, and pollakiuria.

6 Rash was reported during the postmarketing 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.

SU = sulphonylurea

### Description of selected adverse reactions

#### Hypoglycaemia

**Saxagliptin/dapagliflozin combination:** The incidence of hypoglycaemia was low (1.4 %) in the saxagliptin plus dapagliflozin plus metformin group, 0.3 % in the saxagliptin plus metformin group, and 1.8 % in the dapagliflozin plus metformin group. No episodes of major hypoglycaemia were reported, and no subject discontinued the study treatment due to hypoglycaemia (see sections 4.4 and 4.5).

#### Volume depletion

**Saxagliptin/dapagliflozin combination:** Events related to volume depletion (hypotension, dehydration, and hypovolemia) were reflective of the adverse events with dapagliflozin and 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/1.73m² compared to 93.6 ml/min/1.73m² 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/1.73m² in the saxagliptin plus dapagliflozin plus metformin group, -0.46 ml/min/1.73 m² in saxagliptin plus metformin, and 0.81 ml/min/1.73m² in dapagliflozin plus metformin.

Dapagliflozin: In the 13-study, short-term, placebo-controlled pool, reported terms referring to events related to decreased renal function were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This group of events was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 ml/min/1.73m²), events related to decreased renal function were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with baseline eGFR ≥ 30 and < 60 ml/min/1.73m² these events were reported in 18.5% and 9.3% of patients with dapagliflozin 10 mg or placebo. Serum creatinine was further evaluated in those patients with events related to decreased renal function, and most observed increases in creatinine were ≤ 0.5 mg/dl from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

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.

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.

Cardiovascular safety

Saxagliptin/dapagliflozin combination: 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.

Malignancies

Saxagliptin/dapagliflozin combination: Malignant and unspecified neoplasms were reported in 3 subjects included in the pooled safety data. They included adverse events of gastric neoplasm, pancreatic cancer with hepatic metastases, and invasive ductal breast carcinoma in the saxagliptin plus
dapagliflozin plus metformin group. Considering the short latency between first drug exposure and tumour diagnosis, a causal relationship to any specific tumour type is considered unlikely.

**Dapagliflozin:** In the 21-study active- and placebo-controlled pool, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.50 %) and placebo/comparator (1.50 %), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. The numerical imbalance of breast, bladder and prostate tumours must be considered with caution; it will be further investigated in post-authorisation studies.

**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 1169 subjects treated in the pooled safety data from the 3 clinical trials, 1007 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**

**Saxagliptin/dapagliflozin combination:** There is no information available on overdose with Qtern. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient’s clinical status. Saxagliptin and its major metabolite are removed by haemodialysis (23% of dose over four hours). 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 for Qtern
Qtern 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.

Mechanism of action for saxagliptin
Saxagliptin is a highly potent (Kᵢ: 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.

Mechanism of action for dapagliflozin
Dapagliflozin is a highly potent (Kᵢ: 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 a 2- to 3-fold increase in circulating levels glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic 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 1169 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

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Saxagliptin 5 mg + dapagliflozin 10 mg + metformin N=179²</th>
<th>Saxagliptin 5 mg + metformin N=176²</th>
<th>Dapagliflozin 10 mg + metformin N=179²</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%) at week 24¹</td>
<td>Baseline (mean) 8.93</td>
<td>9.03</td>
<td>8.87</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean³) (95 % Confidence interval [CI])</td>
<td>-1.47 (−1.62, −1.31)</td>
<td>-0.88 (−1.03, −0.72)</td>
<td>-1.20 (−1.35, −1.04)</td>
</tr>
<tr>
<td>Difference from saxagliptin + metformin (adjusted mean³) (95 % CI)</td>
<td>-0.59 (−0.81, −0.37)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Difference from dapagliflozin + metformin (adjusted mean³) (95 % CI)</td>
<td>-0.27 (−0.48, −0.05)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1. LRM = Longitudinal repeated measures (using values prior to rescue).
2. Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
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

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Adjusted mean change from baseline by baseline HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 8.0 %</td>
</tr>
<tr>
<td>Saxagliptin + Dapagliflozin + Metformin</td>
<td>Adjusted mean change from baseline (95 % CI)</td>
</tr>
<tr>
<td>Adjusted mean change from baseline (n=37)</td>
<td>(-0.80)</td>
</tr>
<tr>
<td>(95 % CI)</td>
<td>((-1.12, -0.47))</td>
</tr>
<tr>
<td>Saxagliptin + Metformin</td>
<td>Adjusted mean change from baseline (n=29)</td>
</tr>
<tr>
<td>Adjusted mean change from baseline (n=51)</td>
<td>(-0.69)</td>
</tr>
<tr>
<td>(95 % CI)</td>
<td>((-1.06, -0.33))</td>
</tr>
<tr>
<td>Dapagliflozin + Metformin</td>
<td>Adjusted mean change from baseline (n=37)</td>
</tr>
<tr>
<td>Adjusted mean change from baseline (n=52)</td>
<td>(-0.45)</td>
</tr>
<tr>
<td>(95 % CI)</td>
<td>((-0.77, -0.13))</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Sequential add-on clinical trials</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study MB102129</td>
<td>Study CV181168</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin 10 mg add to saxagliptin 5 mg + metformin (N=160)†</td>
<td>Placebo + saxagliptin 5 mg + metformin (N=160)†</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin 5 mg add to dapagliflozin 10 mg + metformin (N=153)†</td>
<td>Placebo + dapagliflozin 10 mg + metformin (N=162)†</td>
</tr>
<tr>
<td>HbA1c (%) at week 24*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.24</td>
<td>8.16</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean‡) (95 % CI)</td>
<td>−0.82 (−0.96, 0.69)</td>
<td>−0.10 (−0.24, 0.04)</td>
</tr>
<tr>
<td>Difference in HbA1c effect Adjusted mean (95 % CI)</td>
<td>−0.72 (−0.91, −0.53)</td>
<td>−0.35 (−0.52, −0.18)</td>
</tr>
</tbody>
</table>

* LRM = Longitudinal repeated measures (using values prior to rescue).
† N is the number of randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
Saxa=saxagliptin; dapa=dapagliflozin; met=metformin

**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 Qtern resulted in change from baseline for systolic blood pressure ranging from –1.3 to –2.2 mm Hg and for diastolic blood pressure ranging from –0.5 to –1.2 mm Hg caused by Qtern’s 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**

**Dapagliflozin:** A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 34.4% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 67.9% had hypertension. The hazard ratio comparing dapagliflozin to comparator was 0.79 (95% CI: 0.58, 1.07), indicating that in this analysis dapagliflozin is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI and stroke were observed with a hazard ratio of 0.77 (95% CI: 0.54, 1.10).

**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; 3533 with multiple risk factors only) who were randomised to saxagliptin (n=8280) or placebo (n=8212) added to regional standards of care for HbA1c and CV risk factors. The study population included those ≥ 65 years (n=8561) and ≥ 75 years (n=2330), with normal or mild renal impairment (n=13,916) as well as moderate (n=2240) 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].

**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 Qtern compared with independent doses of saxagliptin and dapagliflozin.

The following reflects the pharmacokinetic properties of Qtern 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 Qtern with a high-fat meal decreases dapagliflozin $C_{\text{max}}$ by up to 35 % and prolongs $T_{\text{max}}$ 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. Qtern can be administered with or without food.

Drug interactions:
Saxagliptin/dapagliflozin combination: No drug interaction studies have been performed with Qtern 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 ($C_{\text{max}}$) of saxagliptin and its major metabolite attained within 2 and 4 hours ($T_{\text{max}}$), respectively. The $C_{\text{max}}$ 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 $C_{\text{max}}$ values were 24 ng/ml and 47 ng/ml, respectively. The intra-subject coefficients of variation for saxagliptin $C_{\text{max}}$ and AUC were less than 12 %.

Dapagliflozin: Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations ($C_{\text{max}}$) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin $C_{\text{max}}$ and AUC$_\tau$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 hemodialysis 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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$_{\text{ss}}$ 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**

**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.

**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.

### 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.

Reproductive and developmental toxicity
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 1415 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 1191 times the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1441 times the human values at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<table>
<thead>
<tr>
<th>Tablet core</th>
<th>Microcrystalline cellulose (E460i)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Croscarmellose sodium (E468)</td>
</tr>
<tr>
<td></td>
<td>Lactose, anhydrous</td>
</tr>
<tr>
<td></td>
<td>Magnesium stearate (E470b)</td>
</tr>
</tbody>
</table>
Dental type silica (E551)

Film-coating
Polyvinyl 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 AUTHORITY

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORIZATION 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 AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 15/07/2016
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 AUTHORIZATION

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-151 85 Södertälje
Sweden

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

AstraZeneca GmbH
Tinsdaler Weg 183
22880 Wedel
Germany

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union references 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.

The marketing authorization holder shall submit the first periodic safety update report for this product within 6 months following authorization.

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

• Risk Management Plan (RMP)

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

An updated RMP should be submitted:
• At the request of the European Medicines Agency;
• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
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

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

B. PACKAGE LEAFLET
Qtern 5 mg/10 mg film-coated tablets
saxagliptin/dapagliflozin

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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
2. What you need to know before you take Qtern
3. How to take Qtern
4. Possible side effects
5. How to store Qtern
6. Contents of the pack and other information

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”.

- This medicine is taken by mouth for diabetes.
- This medicine is used if your diabetes cannot be controlled with other oral diabetes medicines, along with diet and exercise.

Qtern is used for a type of diabetes called “type 2 diabetes mellitus” in adult patients (aged 18 years and older). “Type 2 diabetes mellitus” is the type of diabetes that usually starts when you are older. If you have type 2 diabetes, your pancreas does not make enough insulin or your body is not able to use the insulin it produces properly. This leads to a high level of sugar in your blood. 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.

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 Qtern.

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before taking Qtern, and during treatment:
- if you have “type 1 diabetes” (the type that usually starts when you are young, and your body does not produce any insulin).
- if you have or have had a disease of the pancreas.
- if you have moderate or severe kidney problems.
- if you have a condition that reduces your body’s ability to fight infections, such as a disease like AIDS or from medicines that you might take after an organ transplant.
- 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 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 or have had a serious hypersensitivity reaction or is suspected.
- 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 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, ‘Possible side effects’. 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 often get infections of the urinary tract or have a serious infection of the urinary tract, including urosepsis or pyelonephritis, which can cause fever and/or chills, burning sensation when passing water (urinating), blood in urine, pain in your back or side. You should call your doctor, pharmacist or nurse immediately if you experience any of these symptoms.
- if you are 75 years old or older.
- if you are taking a medicine to lower your blood sugar, such as insulin or sulphonylureas.
- if you are taking another medicine for diabetes that contains “pioglitazone”.
- if you have an increase in the amount of red blood cells in your blood, seen in tests.

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 and foot care that you are given by your doctor or nurse.

**Kidney function**

Your kidneys should be checked before you start taking and whilst you are on this medicine.
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 ‘Possible side effects’.
- if you are using medicines containing any of the following active substances:
  - 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 Qtern, do not drive or use any tools or machines. Taking this medicine can cause blood sugar levels to fall too low (hypoglycaemia), which 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.

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.

**Some symptoms need immediate medical attention:**
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 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 (may affect up to 1 in 100 people).
These are signs of dehydration:
  - very dry or sticky mouth, feeling very thirsty
- feeling very sleepy or tired
- passing little or no water (urine)
- fast 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 (may affect up to 1 in 1,000 people)
  These are the signs of diabetic ketoacidosis (see also section 2 Warnings and precautions):
  - increased levels of “ketone bodies” in your urine or blood
  - 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.

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:**

**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)
- changes in the amount of red blood cells in your blood (shown in tests)
- dizziness
- tiredness
- stomach ache
- severe joint pain (articulargia)
- 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)
- 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)
- changes in laboratory tests (for example creatinine renal clearance decreased or haematocrit increased).
- rash

**Uncommon**
- thirst
- constipation
- awakening from sleep at night to pass urine
- dry mouth
- weight decreased
- changes in laboratory blood tests, for example blood creatinine increased or urea increased or elevated triglycerides (known as hypertriglyceridaemia)
- decrease in kidney function
- 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.

**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), anhydrous lactose (see section 2 ‘Qtern contains lactose’), magnesium stearate (E470b), dental type silica (E551).
  - film-coating: polyvinyl 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, 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.

**Marketing Authorisation Holder**

AstraZeneca AB  
SE-151 85 Södertälje  
Sweden

**Manufacturer**

AstraZeneca AB  
Gärtnavägen  
SE-151 85 Södertälje  
Sweden

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

AstraZeneca GmbH  
Tinsdaler Weg 183  
22880 Wedel  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**

AstraZeneca S.A./N.V.  
Tel: +32 2 370 48 11

**Lietuva**

UAB AstraZeneca Lietuva  
Tel: +370 5 2660550

**България**

АстраЗенека България ЕООД  
Тел.: +359 2 4455000

**Luxembourg/Luxemburg**

AstraZeneca S.A./N.V.  
Tél/Tel: +32 2 370 48 11

**Česká republika**

AstraZeneca Czech Republic s.r.o.  
Tel: +420 222 807 111

**Magyarország**

AstraZeneca Kft.  
Tel.: +36 1 883 6500

**Danmark**

AstraZeneca A/S  
Tlf: +45 43 66 64 62

**Malta**

Associated Drug Co. Ltd  
Tel: +356 2277 8000
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](http://www.ema.europa.eu)