Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dapagliflozin/Metformin Krka 5 mg/1000 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg dapagliflozin (from dapagliflozin propanediol monohydrate form) and 1 000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Yellow, oval, biconvex, film-coated tablet, marked with K2 on one side of the tablet. Tablet dimensions: 22 x 11 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dapagliflozin/Metformin Krka is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise:

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.

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

4.2 Posology and method of administration

Posology
Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90 mL/min)

The recommended dose is one tablet twice daily. Each tablet contains a fixed dose of dapagliflozin and metformin (see section 2).

For patients insufficiently controlled on metformin monotherapy or metformin in combination with other medicinal products for the treatment of diabetes
Patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes should receive a total daily dose of Dapagliflozin/Metformin Krka equivalent to dapagliflozin 10 mg, plus the total daily dose of metformin, or the nearest therapeutically appropriate dose, already being taken. When Dapagliflozin/Metformin Krka is used in combination with insulin or an insulin secretagogue such as sulphonylurea, a lower dose of insulin or sulphonylurea may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

For patients switching from separate tablets of dapagliflozin and metformin
Patients switching from separate tablets of dapagliflozin (10 mg total daily dose) and metformin to Dapagliflozin/Metformin Krka should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Special populations
Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing medicinal products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3 -6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Dapagliflozin/Metformin Krka is available, individual monocomponents should be used instead of the fixed dose combination.

Table 1. Dosage in patients with renal impairment

GFR mL/min	Metformin	Dapagliflozin
60-89	Maximum daily dose is 3 000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 10 mg.
45-59	Maximum daily dose is 2 000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10 mg.
30-44	Maximum daily dose is 1 000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10 mg. The glucose lowering efficacy of dapagliflozin is reduced.
< 30	Metformin is contraindicated.	Maximum daily dose is 10 mg. Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. The glucose lowering efficacy of dapagliflozin is likely absent.

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly (≥ 65 years)
Because metformin is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, this medicinal product should be used with caution as age increases.
Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients (see sections 4.3 and 4.4).

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

Method of administration
Dapagliflozin/Metformin Krka should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3 Contraindications

Dapagliflozin/Metformin Krka is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (GFR < 30 mL/min) (see sections 4.2, 4.4 and 5.2);
- acute conditions with the potential to alter renal function such as:
    - dehydration,
    - severe infection,
    - shock;

- acute or chronic disease which may cause tissue hypoxia such as:

    - cardiac or respiratory failure,
    - recent myocardial infarction,
    - shock;

- hepatic impairment (see sections 4.2, 4.4 and 5.2);
- acute alcohol intoxication, alcoholism (see section 4.5).

4.4 Special warnings and precautions for use

Lactic acidosis
Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), Dapagliflozin/Metformin Krka should be temporarily discontinued and contact with a healthcare professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and non-steroidal anti-inflammatory drugs [NSAIDs]) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or caregivers should be informed on the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Dapagliflozin/Metformin Krka and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio.

Patients with known or suspected mitochondrial diseases:
In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease. In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Renal function
The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with GFR < 45 mL/min and is likely absent in patients with severe renal impairment (see sections 4.2, 5.1 and 5.2).
Metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis (see section 4.4). Renal function should be assessed before initiation of treatment and regularly thereafter (see section 4.2). Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti-hypertensive or diuretic therapy or when starting treatment with a NSAID.

Use in patients at risk for volume depletion and/or hypotension
Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). It may be more pronounced in patients with high blood glucose concentrations.

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

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is

recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Diabetic ketoacidosis
Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). 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 dapagliflozin should be discontinued immediately.

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

Before initiating dapagliflozin, 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/Metformin Krka in patients with type 1 diabetes have not been established and Dapagliflozin/Metformin Krka should not be used for treatment of patients with type 1 diabetes. In type 1 diabetes mellitus studies, DKA was reported with common frequency.

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

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

Urinary tract infections
Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of treatment should be considered when treating pyelonephritis or urosepsis.

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

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

Cardiac failure
Experience with dapagliflozin in New York Heart Association (NYHA) class IV is limited.

Increased haematocrit
Increased haematocrit has been observed with dapagliflozin treatment (see section 4.8). Patients with pronounced elevations in haematocrit should be monitored and investigated for underlying haematological disease.

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

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

Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Dapagliflozin/Metformin Krka should be discontinued prior to, or at the time of, the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.5).

Surgery
Dapagliflozin/Metformin Krka must be discontinued at the time of surgery with general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Change in clinical status of patients with previously controlled type 2 diabetes
As this medicinal product contains metformin, a patient with type 2 diabetes previously well-controlled on it who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis.
Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.

Vitamin B_{12} decrease/deficiency
Metformin may reduce vitamin B_{12} serum levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. In case of suspicion of vitamin B_{12} deficiency (such as anaemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

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

4.5 Interaction with other medicinal products and other forms of interaction

Coadministration of multiple doses of dapagliflozin and metformin does not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects.

No interaction studies have been performed for Dapagliflozin/Metformin Krka. The following statements reflect the information available on the individual active substances.

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

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin (see sections 4.2 and 4.8).

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

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

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

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

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

Effect of dapagliflozin on other medicinal products
Dapagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after dapagliflozin initiation. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

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

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

Paediatric population
Interaction studies have only been performed in adults.

Metformin
Concomitant use not recommended
Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and Cmax by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are coadministered.

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in the case of fasting, malnutrition or hepatic impairment due to the metformin active substance of this medicinal product (see section 4.4). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Dapagliflozin/Metformin Krka must be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the glucose-lowering medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with metformin (see sections 4.2 and 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Dapagliflozin/Metformin Krka or dapagliflozin in pregnant women. Studies in rats treated with dapagliflozin have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 5.3). Therefore, the use of this medicinal product is not recommended during the second and third trimesters of pregnancy. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3).

When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

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

This medicinal product should not be used while breast-feeding.

Fertility
The effect of this medicinal product or dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Dapagliflozin/Metformin Krka has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

4.8 Undesirable effects

Dapagliflozin/Metformin Krka has been demonstrated to be bioequivalent with coadministered dapagliflozin and metformin (see section 5.2). There have been no therapeutic clinical trials conducted with Dapagliflozin/Metformin Krka tablets.

Dapagliflozin plus metformin

Summary of the safety profile

In an analysis of 5 placebo-controlled dapagliflozin add-on to metformin studies, the safety results were similar to that of the pre-specified pooled analysis of 13 placebo-controlled dapagliflozin studies (see Dapagliflozin, *Summary of the safety profile* below). No additional adverse reactions were identified for the dapagliflozin plus metformin group compared with those reported for the individual components. In the separate dapagliflozin add-on to metformin pooled analysis, 623 subjects were treated with dapagliflozin 10 mg as add-on to metformin and 523 were treated with placebo plus metformin.

Dapagliflozin

Summary of the safety profile

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

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

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

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

Tabulated list of adverse reactions

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

Table 2. Adverse reactions in dapagliflozin and metformin immediate-release clinical trial and post-marketing data[a]

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] Urinary tract infection[*,b,d]	Fungal infection[**]		Necrotising fasciitis of the perineum (Fournier's gangrene)[b,j]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]	Vitamin B_{12} decrease/deficiency[j,§]	Volume depletion[b,e] Thirst[**]	Diabetic ketoacidosis[b,j,k]	Lactic acidosis
Nervous system disorders		Taste disturbance[§] Dizziness			
Gastrointestinal disorders	Gastro-intestinal symptoms[h,§]		Constipation[**] Dry mouth[**]		
Hepatobiliary disorders					Liver function disorders[§] Hepatitis[§]
Skin and subcutaneous tissue disorders		Rash[l]			Urticaria[§] Erythema[§] Pruritus[§]
Musculo-skeletal and connective tissue disorders		Back pain[*]			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia[**]		Tubulo-interstitial nephritis

Reproductive system and breast disorders			Vulvovaginal pruritus[**] Pruritus genital[**]		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[i]	Blood creatinine increased during initial treatment[**,b] Blood urea increased[**] Weight decreased[**]		

[a]The table shows adverse reactions identified from up to 24-week (short-term) data regardless of glycaemic rescue, except those marked with § (see below).
[b]See corresponding subsection below for additional information.
[c]Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.
[d]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.
[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.
[f]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.
[g]Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus -0.33% for placebo. Haematocrit values > 55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.
[h]Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
[i]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus –1.0%; triglycerides -2.7% versus -0.7%.
[j]See section 4.4.
[k]Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.
[l]Adverse reaction was identified through post-marketing surveillance with the use of dapagliflozin. Rash includes the following preferred terms, listed in order of frequency in clinical trials: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical trials (dapagliflozin, N=5 936, All control, N=3 403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.
[*]Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.
[**]Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.
[§]Adverse reaction and frequency categories for metformin are based on information from the metformin Summary of Product Characteristics available in the European Union.

Description of selected adverse reactions

Dapagliflozin plus metformin

Hypoglycaemia

In studies with dapagliflozin in add-on combination with metformin, minor episodes of hypoglycaemia were reported at similar frequencies in the group treated with dapagliflozin 10 mg plus metformin (6.9%) and in the placebo plus metformin group (5.5%). No major events of hypoglycaemia were reported. Similar observations were made for the combination of dapagliflozin with metformin in drug-naive patients.

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

Dapagliflozin

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded

to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

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

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

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

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

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

For studies of dapagliflozin as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. In a study with add-on insulin therapy, higher rates of hypoglycaemia were observed (see section 4.5).

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

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

Volume depletion
In the 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo (see section 4.4).

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

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

Urinary tract infections
In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin compared with placebo (4.7% versus 3.5%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

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

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

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 44 micromoles/L (≤ 0.5 mg/dL) from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Removal of dapagliflozin by haemodialysis has not been studied. The most effective method to remove metformin and lactate is haemodialysis.

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

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Metformin
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD15.

Mechanism of action
Dapagliflozin/Metformin Krka combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin
Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure.
This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function, and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect. Other effects include an increase in haematocrit and reduction in body weight.

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1 400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Metformin
Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
- by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation in muscle;
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

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

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

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

The pharmacodynamics of 5 mg dapagliflozin twice daily and 10 mg dapagliflozin once daily were compared in healthy subjects. The steady-state inhibition of renal glucose reabsorption and the amount of urinary glucose excretion over a 24-hour period was the same for both dosing regimens.

Metformin

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

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

The coadministration of dapagliflozin and metformin has been studied in subjects, with type 2 diabetes, inadequately controlled on diet and exercise alone, and in subjects inadequately controlled on metformin alone or in combination with a DPP-4 inhibitor (sitagliptin), sulphonylurea or insulin. Treatment with dapagliflozin plus metformin at all doses produced clinically relevant and statistically significant improvements in HbA1c and fasting plasma glucose (FPG) compared with control. Clinically relevant glycaemic effects were sustained in long-term extensions up to 104 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI). Additionally, at week 24, clinically relevant and statistically significant improvements in mean changes from baseline in body weight were seen with dapagliflozin and metformin combination treatments compared with control. Body weight reductions were sustained in long-term extensions up to 208 weeks. Additionally, dapagliflozin twice-daily treatment added to metformin was shown to be effective and safe in type 2 diabetic subjects. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

In the DECLARE study, dapagliflozin as adjunct to standard care therapy reduced cardiovascular and renal events in patients with type 2 diabetes.

Glycaemic control
Add-on combination therapy
In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), dapagliflozin 10 mg was evaluated as add-on therapy to metformin compared with a sulphonylurea (glipizide) as add-on therapy to metformin in subjects with inadequate glycaemic control
(HbA1c > 6.5% and ≤ 10%). The results showed a similar mean reduction in HbA1c from baseline to week 52, compared with glipizide, thus demonstrating non-inferiority (Table 3). At week 104, adjusted mean change from baseline in HbA1c was -0.32% for dapagliflozin and -0.14% for glipizide, respectively. At week 208, adjusted mean change from baseline in HbA1c was -0.10% for dapagliflozin and 0.20% for glipizide, respectively. At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%, 4.3% and 5.0%, respectively) experienced at least one event of hypoglycaemia compared with the group treated with glipizide (40.8%, 47% and 50.0%, respectively). The proportion of subjects remaining in the study at week 104 and week 208 was 56.2% and 39.7% for the group treated with dapagliflozin and 50.0% and 34.6% for the group treated with glipizide.

Table 3. Results at week 52 (LOCF[a]) inanactive-controlled study comparing dapagliflozin with glipizide as add-on to metformin

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

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

*p-value < 0.0001

Dapagliflozin as an add-on with either metformin alone, metformin in combination with sitagliptin, sulphonylurea or insulin (with or without additional oral glucose-lowering medicinal products, including metformin) resulted in statistically significant mean reductions in HbA1c at 24 weeks compared with subjects receiving placebo (p < 0.0001; Tables 4, 5 and 6). Dapagliflozin 5 mg twice daily provided statistically significant reductions in HbA1c at 16 weeks compared with subjects receiving placebo (p < 0.0001; Table 4).

The reductions in HbA1c observed at week 24 were sustained in the add-on combination studies. For the add-on to metformin study, HbA1c reductions were sustained through week 102 (-0.78% and 0.02% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively). At week 48 for metformin plus sitagliptin, the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.44% and 0.15%, respectively. At week 104 for insulin (with or without additional oral glucose-lowering medicinal products, including metformin), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively. At weeks 48 and 104, the insulin dose remained stable compared to baseline in subjects treated with dapagliflozin 10 mg at an average dose of 76 IU/day. In the placebo group there was an increase of 10.5 IU/day and 18.3 IU/day from baseline (mean average dose of 84 and 92 IU/day) at weeks 48 and 104, respectively. The proportion of subjects remaining in the study at week 104 was 72.4% for the group treated with dapagliflozin 10 mg and 54.8% for the placebo group.

In a separate analysis of subjects on insulin plus metformin, similar reductions in HbA1c to those seen in the total study population were seen in subjects treated with dapagliflozin with insulin plus metformin. At week 24, HbA1c change from baseline in subjects treated with dapagliflozin plus insulin with metformin was -0.93%.

Table 4. Results of (LOCF[a]) placebo-controlled studies up to 24 weeks of dapagliflozin in add-on combination with metformin or metformin plus sitagliptin

	Add-on combination					
	Metformin[1]		**Metformin**[1,b]		**Metformin**[1]**+sitagliptin**[2]	
	Dapagliflozin 10 mg QD	**Placebo QD**	**Dapagliflozin5 mg BID**	**Placebo BID**	**Dapagliflozin 10 mg QD**	**Placebo QD**
Nc	135	137	99	101	113	113
HbA1c(%) Baseline (mean)	7.92	8.11	7.79	7.94	7.80	7.87
Change from baseline[d]	-0.84	-0.30	-0.65	-0.30	-0.43	-0.02
Difference from placebo[d]	-0.54*		-0.35*		-0.40*	
(95% CI)	(-0.74, -0.34)		(-0.52, -0.18)		(-0.58, -0.23)	
Subjects(%) achieving: HbA1c<7% Adjusted for baseline	40.6**	25.9	38.2** (N=90)	21.4 (N=87)		
Body weight (kg) Baseline (mean) Change from baseline[d]	86.28	87.74	93.62	88.82	93.95	94.17
	-2.86	-0.89	-2.74	-0.86	-2.35	-0.47
	-1.97*		-1.88***		-1.87*	

Difference from placebo[d]						
(95% CI)	(-2.63, -1.31)		(-2.52, -1.24)		(-2.61, -1.13)	

Abbreviations: QD: once daily; BID: twice daily
[1]Metformin ≥ 1 500 mg/day
[2]Sitagliptin 100 mg/day
[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward
[b]Placebo-controlled 16-week study
[c]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period
[d]Least squares mean adjusted for baseline value
*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product
**p-value < 0.05 versus placebo + oral glucose-lowering medicinal product
***The percent change in body weight was analysed as a key secondary endpoint (p < 0.0001); absolute body weight change (in kg) was analysed with a nominal p-value (p < 0.0001).

Table 5. Results of a 24-week placebo-controlled study of dapagliflozinin add-on combination with metformin and a sulphonylurea

	Add-oncombination	
	Sulphonylurea +metformin[1]	
	Dapagliflozin 10 mg	**Placebo**
Na	108	108
HbA1c(%)[b`] Baseline (mean)	8.08	8.24
Change from Baseline[c] Difference from Placebo[c]	-0.86 -0.69*	-0.17
(95% CI)	(-0.89, -0.49)	
Subjects(%)achieving: HbA1c < 7% Adjusted for baseline	31.8*	11.1
Bodyweight(kg)		
Baseline (mean)	88.57	90.07
Change from Baseline[c] Difference from Placebo[c]	-2.65 -2.07*	-0.58
(95% CI)	(-2.79, -1.35)	

[1]Metformin (immediate- or extended-release formulations) ≥ 1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrolment. [a]Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement. [b]HbA1c analysed using LRM (Longitudinal repeated measures analysis)
[c]Least squares mean adjusted for baseline value
*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product(s)

Table 6. Results at week 24 (LOCF[a]) in a placebo-controlled study of dapagliflozin in combination with insulin (alone or with oral glucose-lowering medicinal products,including metformin)

Parameter	**Dapagliflozin10 mg +insulin ±oralglucose-lowering medicinal products[2]**	**Placebo +insulin ±oralglucose-lowering medicinal products[2]**
N[b]	194	193
HbA1c(%)		
Baseline (mean)	8.58	8.46
Change from baseline[c] Difference from placebo[c]	-0.90 -0.60*	-0.30
(95% CI)	(-0.74, -0.45)	
Bodyweight (kg)		

Baseline (mean)	94.63	94.21
Change from baseline[c] Difference from placebo[c]	-1.67 -1.68*	0.02
(95% CI)	(-2.19, -1.18)	
Mean daily insulin dose (IU)[1] Baseline (mean)	77.96	73.96
Change from baseline[c] Difference from placebo[c]	-1.16 -6.23*	5.08
(95% CI)	(-8.84, -3.63)	
Subjects with mean daily insulin dose reduction of at least	19.7**	11.0
10% (%)		

[a]LOCF: Last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward
[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short- term double-blind period
[c]Least squares mean adjusted for baseline value and presence of oral glucose-lowering medicinal product
*p-value < 0.0001 versus placebo + insulin ± oral glucose-lowering medicinal product
**p-value < 0.05 versus placebo + insulin ± oral glucose-lowering medicinal product
[1]Up-titration of insulin regimens (including short-acting, intermediate, and basal insulin) was only allowed if subjects met pre-defined FPG criteria.
[2]Fifty percent of subjects were on insulin monotherapy at baseline; 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group, 80% were on metformin alone, 12% were on metformin plus sulphonylurea therapy, and the rest were on other oral glucose-lowering medicinal products.

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

Treatment with dapagliflozin 10 mg in combination with metformin (up to 2 000 mg per day) provided significant improvements in HbA1c compared to the individual components (Table 7), and led to greater reductions in FPG (compared to the individual components) and body weight (compared to metformin).

Table 7. Results at week 24 (LOCFa) in an active-controlled study of dapagliflozin and metformin combination therapy in drug-naive patients

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

[a]*LOCF: last observation (prior to rescue for rescued patients) carried forward.*
[b]All randomised patients who took at least one dose of double-blind study medicinal product during the short- term double-blind period.
[c]Least squares mean adjusted for baseline value.
*p-value < 0.0001.

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

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

	Dapagliflozin10 mg QD	**Dapagliflozin10 mg QD**	**Prolonged-release exenatide 2 mg**
	+	**+**	**+ QW**
	prolonged-release	**placeboQW**	
Parameter	**exenatide2 mg QW**		**placeboQD**
N	**228**	**230**	**227**
HbA1c(%)			
Baseline (mean)	9.29	9.25	9.26
Change from baseline[a]	-1.98	-1.39	-1.60
Mean difference in change			
from baseline between		-0.59*	-0.38**
combination and single		(-0.84, -0.34)	(-0.63, -0.13)
active agent (95% CI)			
Subjects(%)achieving HbA1c< 7%	44.7	19.1	26.9
Bodyweight(kg)			
Baseline (mean)	92.13	90.87	89.12
Change from baseline [a]	-3.55	-2.22	-1.56
Mean difference in change			
from baseline between		-1.33*	-2.00*
combination and single		(-2.12, -0.55)	(-2.79, -1.20)
active agent (95% CI)			

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

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

Fasting plasma glucose
Treatment with dapagliflozin as an add-on to either metformin alone (dapagliflozin 10 mg QD or dapagliflozin 5 mg BID) or metformin plus sitagliptin, sulphonylurea or insulin resulted in statistically significant reductions in FPG (-1.90 to -1.20 mmol/L [-34.2 to -21.7 mg/dL]) compared with placebo (-0.58 to 0.18 mmol/L [-10.4 to 3.3 mg/dL]) at week 16 (5 mg BID) or week 24. This effect was observed at week 1 of treatment and maintained in studies extended through week 104.

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

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

Post-prandial glucose
Treatment with dapagliflozin 10 mg as an add-on to sitagliptin plus metformin resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to week 48.
Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in significantly greater reductions in 2-hour post-prandial glucose at week 28 compared to either agent alone.

Body weight
Dapagliflozin as an add-on to metformin alone or metformin plus sitagliptin, sulphonylurea or insulin (with or without additional oral glucose-lowering medicinal products, including metformin) resulted in statistically significant body weight reduction up to 24 weeks (p < 0.0001, Tables 4, 5 and 6). These effects were sustained in longer-term trials. At 48 weeks, the difference for dapagliflozin as add-on to metformin plus sitagliptin compared with placebo was -2.07vkg. At 102 weeks, the

difference for dapagliflozin as add-on to metformin compared with placebo or as add-on to insulin compared with placebo was -2.14 and -2.88 kg, respectively.

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

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

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

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

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

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

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

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

Glycaemic control in patients with moderate renal impairment CKD3A (eGFR ≥ 45 to < 60 mL/min/1.73m²)
The efficacy of dapagliflozin was assessed in a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m^2 who had inadequate glycaemic control on usual care. Treatment with dapagliflozin resulted in reductions in HbA1c and body weight compared with placebo (Table 9).

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

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

placebo[c]		
(95% CI)	(-2.15, -0.69)	

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

Cardiovascular and renal outcomes
Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomised, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional cardiovascular risk factors (age ≥ 55 years in men or ≥ 60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use) or established cardiovascular disease.
Of 17 160 randomised patients, 6 974 (40.6%) had established cardiovascular disease and 10 186 (59.4%) did not have established cardiovascular disease. 8 582 patients were randomised to dapagliflozin 10 mg and 8 578 to placebo, and were followed for a median of 4.2 years.
The mean age of the study population was 63.9 years, 37.4% were female. In total, 22.4% had had diabetes for ≤ 5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

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

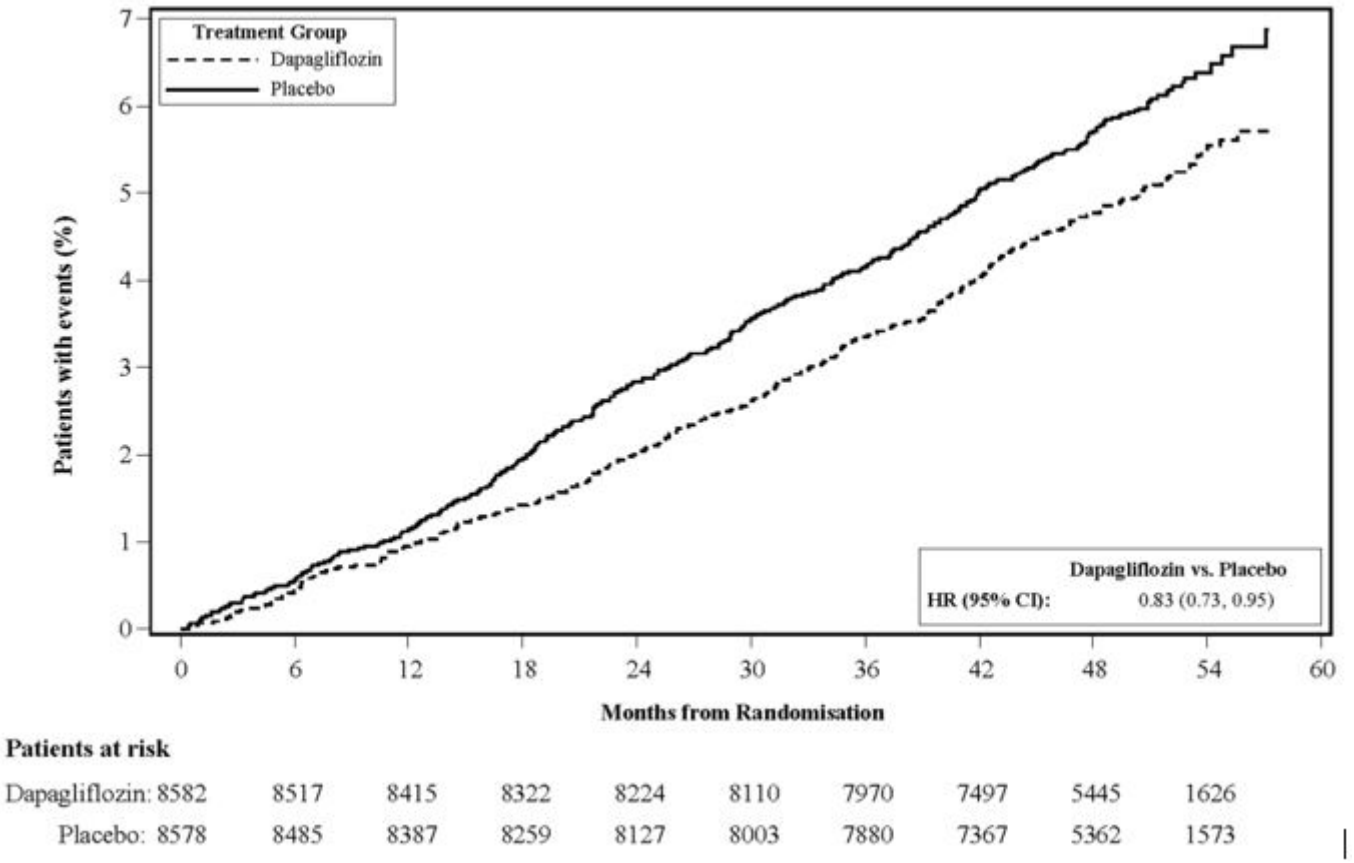
Most patients (98%) used one or more diabetic medicinal products at baseline, including metformin (82%), insulin (41%) and sulfonylurea (43%).

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

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

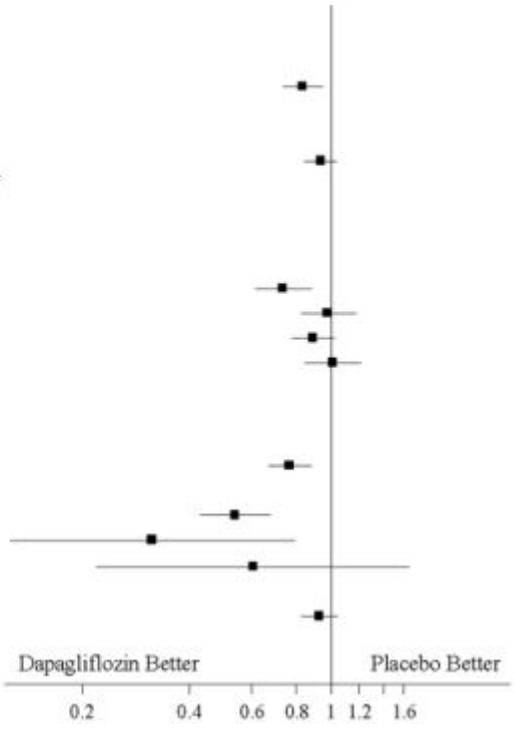
Heart failure or cardiovascular death
Dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalisation for heart failure or cardiovascular death (Figure 1). The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death (Figure 2).
The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established cardiovascular disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR) and region.

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



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

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



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

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

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

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

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

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

Metformin
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1 000 patient-years) versus diet alone (43.3 events/1 000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1 000 patient-years), p=0.0034;
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1 000 patient-years, diet alone 12.7 events/1 000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1 000 patient-years versus diet alone 20.6 events/1 000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1 000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1 000 patient-years, diet alone 18 events/1 000 patient-years, (p=0.01).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with dapagliflozin/metformin 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

Dapagliflozin/Metformin Krka combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride administered together as individual tablets.

The pharmacokinetics of 5 mg dapagliflozin twice daily and 10 mg dapagliflozin once daily were compared in healthy subjects. Administration of 5 mg dapagliflozin twice daily gave similar overall exposures (AUCss) over a 24-hour period as 10 mg dapagliflozin administered once daily. As expected, dapagliflozin 5 mg administered twice daily compared with 10 mg dapagliflozin once daily resulted in lower peak dapagliflozin plasma concentrations (C^{max}) and higher trough plasma dapagliflozin concentrations (C^{min}).

Interaction with food
The administration of this medicinal product in healthy volunteers after a high fat meal compared to after the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin. The meal resulted in a delay of 1 to 2 hours in the peak concentrations and a decrease in the maximum plasma concentration of 29% of dapagliflozin and 17% of metformin. These changes are not considered to be clinically meaningful.

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

The following statements reflect the pharmacokinetic properties of the individual active substances of this medicinal product.

Dapagliflozin

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C^{max}) were usually attained within 2 hours after administration in the fasted state.

Geometric mean steady-state dapagliflozin C^{max} and AUCτ 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

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

Biotransformation

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Elimination

The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [^{14}C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

Linearity

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

Special populations

Renal impairment

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of haemodialysis on dapagliflozin exposure is not known.

Hepatic impairment

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared with healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean Cmax and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Elderly(≥ 65years)

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

The mean dapagliflozin AUCss in females was estimated to be about 22% higher than in males.

Race

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

Bodyweight

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.

Paediatric population
Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.

Metformin
Absorption
After an oral dose of metformin, tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 µg/mL, even at maximum doses.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Biotransformation
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

Special populations
Renal impairment
In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

Coadministration of dapagliflozin and metformin
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

The following statements reflect the preclinical safety data of the individual active substances of Dapagliflozin/Metformin Krka.

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

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

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

In a separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed *in utero* and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were

1 415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

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

Metformin
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Copovidone
Croscarmellose sodium
Microcrystalline cellulose
Magnesium stearate

Film coating
Poly(vinyl alcohol)
Calcium carbonate
Macrogol
Talc
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blister (PVC/PVDC/PVC//Alu) in a box containing 14, 28, 56, 60 or 196 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/118/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th August 2025

10 DATE OF REVISION OF THE TEXT

July 2026