SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Dapagliflozin 5 mg Adco film-coated tablets
Dapagliflozin 10 mg Adco film-coated tablets

DAPAGLIFLOZIN ADCO IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES MELLITUS. DAPAGLIFLOZIN ADCO IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES. IT IS NOT INDICATED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS AND HEART FAILURE.

There have been reports of metabolic acidosis, including ketoacidosis, which were serious life-threatening or fatal, in patients taking Dapagliflozin Adco.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 14 mmol/L. Dapagliflozin Adco should be discontinued and the patient should be promptly evaluated and managed accordingly.

Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with Dapagliflozin Adco.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g., history of pancreatitis or pancreatic surgery. Dapagliflozin Adco is contraindicated in these patients.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dapagliflozin 5 mg Adco: Each film-coated tablet contains 5 mg dapagliflozin.
Dapagliflozin 10 mg Adco: Each film-coated tablet contains 10 mg dapagliflozin.
Sugar free.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets
Dapagliflozin 5 mg Adco: Yellow coloured, round, biconvex, film-coated tablets debossed with "D1" on one side and "M" on other side.
Dapagliflozin 10 mg Adco: Yellow coloured, diamond, biconvex, film-coated tablets debossed with "D2" on one side and "M" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus

Dapagliflozin Adco is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- as monotherapy as an adjunct to diet and exercise to improve glycaemic control
- as add-on combination therapy, with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin, when these, together with diet and exercise, do not provide adequate glycaemic control
- to reduce the risk of developing new or worsening existing heart failure or cardiovascular death in patients with established cardiovascular (CV) disease or multiple CV risk factors.

Heart failure

Dapagliflozin Adco is indicated in adults to reduce the risk of worsening heart failure or cardiovascular death, in patients with heart failure (NYHA class II-IV), and with a left ventricular ejection fraction (LVEF) ≤ 40 %.

4.2 Posology and method of administration

Posology

Type 2 diabetes mellitus

Monotherapy and add-on combination therapy

The recommended dose is 10 mg Dapagliflozin Adco once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin. The recommended starting doses of Dapagliflozin Adco and metformin when used as initial combination therapy are 10 mg Dapagliflozin Adco plus 500 mg metformin once daily. Patients with inadequate glycaemic control on this starting dose should have their metformin dose increased according to approved metformin product information.

Use with medicines known to cause hypoglycaemia

When Dapagliflozin Adco is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Heart failure

The recommended dose of Dapagliflozin Adco is 10 mg taken orally once daily at any time of the day regardless of meals. Dapagliflozin Adco can be used in conjunction with other heart failure therapies.

Special Populations

Renal impairment:

No dosage adjustment is required based on renal function.

In patients with diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced in

patients with eGFR < 45 mL/min/1,73 m^2 (see section 4.4). Therefore, if eGFR falls below 45 mL/min/1,73 m^2, additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus if further glycaemic control is needed. Treatment with dapagliflozin should be continued for management of renal and cardiovascular comorbidities.

Monitoring of renal function is recommended as follows:
- Prior to initiation of Dapagliflozin Adco and at least annually, thereafter.
- Prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.

Hepatic impairment*:*
No dosage adjustment for Dapagliflozin Adco is necessary for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Dapagliflozin Adco is not recommended for patients with severe hepatic impairment as efficacy has not been established (see section 5.2).

Elderly*:*
No dosage adjustment for Dapagliflozin Adco is required based on age (see section 4.4).

Paediatric population
Safety and effectiveness of Dapagliflozin Adco in paediatric and adolescent patients have not been established. No data is available.

Method of administration
For oral administration.

4.3 Contraindications
- Hypersensitivity to dapagliflozin or to any of the excipients of Dapagliflozin Adco as listed in section 6.1.

- Diabetes mellitus Type 1.
- Pregnant women or women who are breastfeeding their infants (see section 4.6).
- Patients with a history of pancreatitis or pancreatic surgery (see section 4.4).

4.4 Special warnings and precautions for use
General:
Dapagliflozin Adco may cause a decrease in systolic blood pressure and diastolic blood pressure.
Dapagliflozin Adco should not be used for the treatment of diabetic ketoacidosis.

Renal impairment:

There is limited experience with Dapagliflozin Adco in patients with severe renal impairment (eGFR < 25 mL/min/1,73 m^2) or end-stage renal disease (ESRD). Dapagliflozin Adco is not recommended for the treatment of type 2 diabetes mellitus to improve glycaemic control when eGFR is persistently below
45 mL/min/1,73 m^2 as the glycaemic efficacy of dapagliflozin is dependent on renal function (see section 4.2). However, treatment with Dapagliflozin Adco should be continued for the management of renal and cardiovascular comorbidities and additional glucose lowering treatment should be considered if further glycaemic control is needed.

The renal function should be monitored as follows:

- prior to initiation of Dapagliflozin Adco and at least yearly thereafter.
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- for renal function approaching eGFR 45 mL/min/1,73 m^2, at least 2 to 4 times per year.

If the renal function falls persistently below eGFR < 45 mL/min/1,73 m^2, treatment with Dapagliflozin Adco should be discontinued (see section 4.3).

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

Use in patients at risk for volume depletion and/or hypotension:
Due to its mechanism of action, dapagliflozin, as contained in Dapagliflozin Adco, increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations.

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

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

Diabetic ketoacidosis:
Cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases have been reported in patients treated with sodium-glucose co-transporter 2 inhibitors, including dapagliflozin. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, such as Dapagliflozin Adco should be used with caution in patients with increased risk of Diabetic ketoacidosis (DKA). Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve

(e.g., type 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 experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

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. If ketoacidosis is suspected, Dapagliflozin Adco should be discontinued and the patient should be promptly evaluated.

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

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

Dapagliflozin Adco is contraindicated for the treatment of patients with type 1 diabetes mellitus (see section 4.3).

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 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 Adco should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections:
Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of Dapagliflozin Adco 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 antihypertensive medicines 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 and 4.8).

Cardiac failure:
Experience with in Dapagliflozin Adco in NYHA class IV is limited.

Chronic kidney disease:
There is no experience with Dapagliflozin Adco for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria.

Dapagliflozin Adco has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA-associated vasculitis), ongoing or recent requirements of cytotoxic, immunosuppressive or other immunomodulating renal therapy, or in patients who received an organ transplant.

Lower limb amputations:
An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

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

Paediatric population
Safety and efficacy of Dapagliflozin Adco in paediatric patients has not been established.

4.5 Interaction with other medicines and other forms of interaction
Pharmacodynamic interactions
Diuretics
Dapagliflozin Adco 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 Adco in patients with type 2 diabetes mellitus (see sections 4.2 and 4.8).

Pharmacokinetic interactions

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

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

Effect of other medicines on dapagliflozin

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

Following co-administration 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 co-administration 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 medicines

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

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 and dose changes. Please refer the patient to the doctor who prescribed lithium in order to monitor serum concentration of lithium.

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 Dapagliflozin Adco. Use of alternative methods to monitor glycaemic control is advised.

4.6 Fertility, pregnancy and lactation

Pregnancy

Dapagliflozin Adco is contraindicated in pregnancy. Maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, Dapagliflozin Adco should be discontinued (see section 4.3).

Breastfeeding

Mothers on Dapagliflozin Adco should not breastfeed their infants. Dapagliflozin Adco must not be used by a nursing woman. Studies in rats have shown excretion of dapagliflozin in milk. Exposure to Dapagliflozin Adco must be avoided during the first 2 years of life (see section 4.3).

Fertility

The effect of dapagliflozin on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

Dapagliflozin Adco has little or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia (and its effects on their motor skills) when Dapagliflozin Adco is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

a. Summary of the safety profile

Type 2 diabetes mellitus

The most frequently reported adverse reactions were genital infections.

Heart failure

The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

b. Tabulated list of adverse reactions

Infections and infestations	
Frequent:	Vulvovaginitis, balanitis and related genital infections[b,c], Urinary tract infection[b,d], including pyelonephritis, cystitis.
Less frequent:	Fungal infection, Necrotising fasciitis of the perineum (Fournier's gangrene)[b,g]

Metabolism and nutrition disorders	
Frequent:	Hypoglycaemia (when used with SU or insulin)[b]
Less frequent:	Volume depletion[b,e], Thirst, Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,g]
Nervous system disorders	
Frequent:	Dizziness
Gastrointestinal disorders	
Less frequent:	Constipation, Dry mouth
Skin and subcutaneous tissue disorders	
Frequent:	Rash[h]
Less frequent:	Angioedema, Hyperhidrosis
Musculoskeletal and connective tissue disorders	
Frequent:	Back pain
Renal and urinary disorders	
Frequent:	Dysuria, Polyuria[f], glucosuria
Less frequent:	Nocturia, tubulointerstitial nephritis
Reproductive system and breast disorders	
Less frequent:	Vulvovaginal pruritus, Pruritus genital
Investigations	
Frequent:	Haematocrit increased, Creatinine renal clearance decreased during initial treatment[b], Dyslipidaemia
Less frequent:	Blood creatinine increased during initial treatment[b], Blood urea increased, Weight decreased

[a] The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[b] See corresponding subsection below for additional information.

[c] Vulvovaginitis, balanitis and related genital infections includes, e.g., the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess, balanoposthitis, genitourinary tract infection, penile abscess, posthitis.

[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] See section 4.4

[h] Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular,

rash vesicular, and rash erythematous.

c. Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

Vulvovaginitis, balanitis and related genital infections were reported in patients treated with dapagliflozin. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and less frequently 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.

Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.

Necrotising fasciitis of the perineum (Fournier's gangrene)

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

Hypoglycaemia

The frequency of hypoglycaemia is depended on the type of background therapy used in the clinical studies in diabetes mellitus.

For dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar between all treatment groups. Across all studies, major events of hypoglycaemia were less frequent and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia (see section 4.5).

Urinary tract infections

Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and less frequently 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.

Increased creatinine

Adverse reactions related to increased creatinine (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate) was reported. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1,73 m^2.

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 0,5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

Laboratory findings
Serum inorganic phosphorous
Increases from baseline in mean serum phosphorus levels were reported in patients treated with dapagliflozin 10 mg compared to placebo (mean increases of 0,0419 mmol/L vs. 0,0128 mmol/L respectively). The clinical relevance is unknown.

Haematocrit
A moderate increase in haematocrit occurs and may be an indication of volume depletion.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose
In overdose, side effects may be elicited or exacerbated. Appropriate symptomatic and supportive treatment should be initiated as dictated by the patient's clinical status.
The removal of dapagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A 21.2 Oral hypoglycaemics
Pharmacotherapeutic group: Drugs used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors,
ATC code: A10BK01

Dapagliflozin is a reversible inhibitor of sodium glucose co-transporter 2 (SGLT2) that improves glycaemic control in patients with type 2 diabetes mellitus and provides cardio-renal benefits.

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 is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. Secondary effects of SGLT2 inhibition with dapagliflozin also include a modest reduction in volume overload, reduced blood pressure, lower preload and afterload, which may have beneficial effects on cardiac remodelling and may preserve renal function. Other effects include reduction in body weight, and an increase in haematocrit.

The cardio-renal benefits of dapagliflozin are not solely dependent on the blood glucose lowering effect. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis,

adipokines and uric acid may be mechanisms underlying the cardio-renal beneficial effects of dapagliflozin.

Dapagliflozin reduces 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 glomerular filtration rate (GFR). Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging.

SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 1400 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects
The urinary glucose excretion with dapagliflozin results in osmotic diuresis and increases in urinary volume. The increase in urinary volume may be associated with a transient increase in urinary sodium excretion that which may not be associated with changes in serum sodium concentrations.

Dapagliflozin may cause a decrease in systolic blood pressure and diastolic blood pressure.

Urinary uric acid excretion was also increased and accompanied by a reduction in serum uric acid concentration. At 24 weeks, changes in serum uric acid concentrations from baseline ranged from -0,0183 mmol/L to -0,0483 mmol/L.

5.2 Pharmacokinetic properties
Absorption
Dapagliflozin was absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects, Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50 % and prolonged T_{max} by approximately 1 hour but did not alter AUC as compared with the fasted state. These changes are not considered to be

clinically meaningful.

Distribution
Dapagliflozin is approximately 91 % protein bound. Protein binding was not altered in various disease states (e.g., renal or hepatic impairment).

Biotransformation
Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. 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. Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61 % of a 50 mg [^{14}C]-dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42 % [based on AUC $_{(0\text{-}12h)}$] of total plasma radioactivity, similar to the 39 % contribution by parent compound. No other metabolite accounted for > 5 % of the total plasma radioactivity at any time point measured. 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
Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2 % as unchanged dapagliflozin. After administration of 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 compound.

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.

Specific patient groups
Renal impairment:
At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin that were 32 %, 60 % and 87 % higher, respectively, than those of patients with type 2 diabetes mellitus and normal renal function. At dapagliflozin 20 mg once daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The renal glucose clearance and 24-hour glucose excretion was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. 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 patients with type 2 diabetes mellitus and normal renal function

or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known. The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes.

Hepatic impairment:
In patients with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12 % and 36 % higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40 % and 67 % higher than matched healthy controls, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see section 4.4).

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Sodium lauryl sulphate
Crospovidone
Colloidal silicon dioxide

Magnesium stearate

Film-coating

Opadry II 85F32782 Yellow consisting of polyvinyl alcohol - part hydrolysed (E1203), titanium dioxide (E171), macrogol/PEG (E1521), talc (E553b) and iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging until required for use, in order to protect from light.

6.5 Nature and contents of container

The film-coated tablets are packed in:

White HDPE containers with white PP closure and silica gel canister. Pack sizes 30 or 500 tablets.

Alu-Alu blister pack with 10 tablets per blister strip. Three blister strips in an outer cardboard carton. Pack size: 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBERS

Dapagliflozin 5 mg Adco: 57/21.2/0222
Dapagliflozin 10 mg Adco: 57/21.2/0223

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 March 2025

10. DATE OF REVISION OF THE TEXT

To be allocated.